FEBRUARY 1953

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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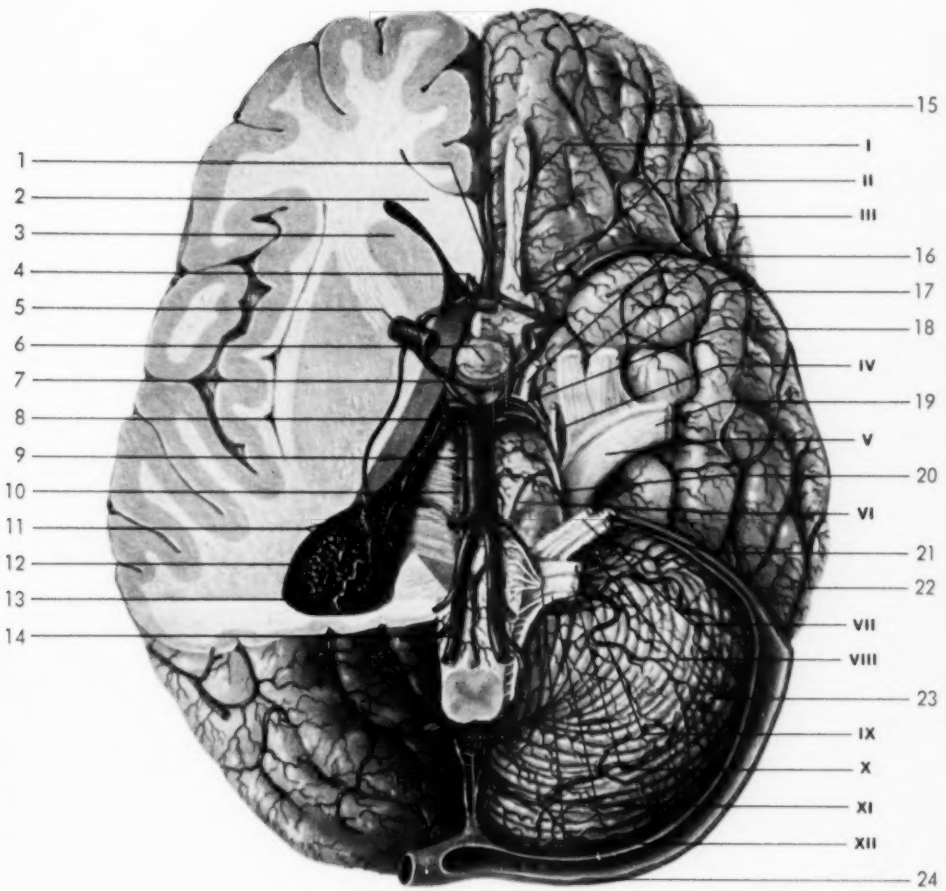

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11. Choroid artery and vein
12. Choroid plexus of lateral ventricle
13. Inferior cornu of lateral ventricle
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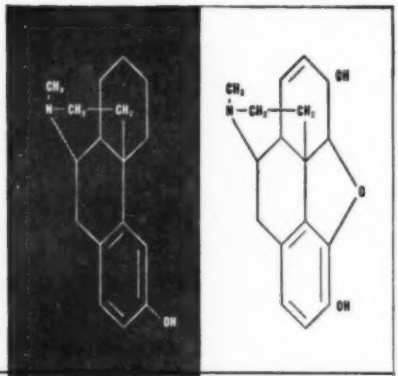

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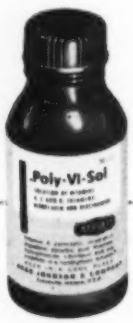

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1. Steinbrocker, O.; Berkowitz, S.; Ehrlich, M.; Elkind, M., and Carp, S.: Paper read before the Annual Meeting of the American Rheumatism Association, Chicago, Ill., June 6, 1952.
2. Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952.
3. Smith, C. H., and Kunz, H. G.: J. M. Soc. New Jersey *49*:306, 1952.

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1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
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[1]Zink, O. C.: Routine Clinical Experiences Using UROKON *70%* in Intravenous Urography (Private Report dated May 12, 1952).
[2]Nesbit, R. M. and Nesbitt, T. E.: Experiences with High Concentration UROKON for Pyelography. Univ. of Mich. Med. Bull. *18*:225 (1952).
[3]Barry, C. N. and Rose, D. K.: UROKON SODIUM *70%* in Excretory Urography, J. Urol. (to be published).

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Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
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BULLETIN OF
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HORMONES OF THE ADRENAL CORTEX*

EDWARD C. KENDALL, Ph.D.

Visiting Professor of Chemistry, Princeton University
James Forrestal Research Center

ON September 21, 1948, cortisone was administered to a patient who had rheumatoid arthritis.[1] During the preceding five years she had continued to become worse and at the time that cortisone was given she was confined to her bed and endured much pain. Within a week she walked out of the hospital in a gay mood and went on a shopping trip for three hours without after-effects. During the following seven months about thirty more patients were given cortisone. The results were reported on April 20, 1949 and before January 1950 the word cortisone was given a place in our vocabulary.

Three and a half years have now passed and from the vantage point of today it is of interest to summarize our knowledge of the hormones of the adrenal cortex. However, the chemical investigation of the gland is not yet complete, and therefore what I shall say tonight is a report of progress. To this end I shall review the successive stages through which the investigation has passed.

* Presented at the 25th Graduate Fortnight of The New York Academy of Medicine, October 7, 1952. This lecture is a modification of a paper presented before the American Philosophical Society in April 1952 and published in the Proceedings of that Society.

Our knowledge of the cortex of the adrenal gland in health and disease has accrued from almost one hundred years of research. In 1855 an English physician, Thomas Addison,[2] reported his observations concerning a group of patients who followed a common course throughout their illness and death. Addison ascribed the cause of death to destruction of the adrenal gland. During the first stage of the investigation which followed the work of Addison it was shown that the inner and outer portions of the gland were entirely different not only in physical nature but also in function. From the inner portion, designated the medulla, epinephrine was isolated in 1901 and was in fact the first hormone to be separated in crystalline form from any of the ductless glands. Epinephrine is a powerful and important agent but removal of the adrenal medulla does not cause death of the animal.[3] The outer portion of the gland, designated the cortex, was shown to be essential for life and seventy-five years after publication of Addison's clinical observations an extract of the cortex was prepared which maintained the life of animals which had been deprived of their adrenal glands.[4, 5] The symptoms of patients who had Addison's disease also were relieved by administration of the extract. Preparation of the extract which was achieved in 1930 brought to a close the first stage of the investigation. At the time it was believed that *the* hormone of the adrenal cortex soon would be isolated in pure form, and it was hoped that treatment of deficiency of the adrenal gland would be as satisfactory as was treatment of diabetes with insulin. No one could foresee that almost twenty years would pass before the chemist could provide an answer which was satisfactory although not in final form.

The second stage of the investigation has to do with the relationship between the secretion of the adrenal cortex and the retention and distribution of sodium and chloride in the body. Extensive research had shown that the metabolism of sodium and chloride was under close control. It was known that the blood and fluids in the body contained relatively high concentrations of these mineral constituents. The muscle and other tissues of the body at all times contained much less.[3] If the daily intake of salt was large the excess did not accumulate but was excreted promptly in the urine. If the daily intake of salt was small very little was excreted.[6] The body appeared to have the power to retain salt and to maintain the concentration in the blood within narrow limits. During this phase of the investigation it was discovered that the power

to retain sodium chloride was lost when the adrenal glands were removed from animals.[7] The same phenomenon was then observed in patients.[8] Patients who have Addison's disease are invariably weak, the blood pressure is low, the appetite poor, and the volume of circulating blood may be much less than normal. Nevertheless all these typical symptoms disappear if the sodium chloride which is constantly lost through the kidneys is replaced by a high daily intake of salt in the diet. This observation was of great importance since manufacture of the extract of the adrenal cortex was difficult, the material was scarce and the price was prohibitive except for well-to-do patients. The use of salt to relieve the symptoms of Addison's disease was the tangible contribution of stage two.

The third stage of the investigation disclosed the importance of another constituent of the blood—potassium.[9] Treatment of patients who had Addison's disease with sodium chloride was frequently of great help but few of them enjoyed a sense of well-being. Eventually it was found that potassium was toxic to these persons.[10] Potassium is in all food, for example, potatoes contain a high percentage of potassium; meat, milk and nuts also are rich in potassium. If the diet was controlled rigidly and the intake of potassium was small the patient was relieved of many of the symptoms associated with Addison's disease; however, as this regimen was continued the patient became increasingly sensitive to potassium. Unfortunate consequences followed. On occasions such as Thanksgiving Day or Christmas the patient might partake of turkey or nuts and within a few hours a serious crisis sometimes developed which led to prostration and death unless an extract of the adrenal cortex was administered. Life under these conditions was precarious and the outlook for these patients was not hopeful.

The first three stages of the conquest of the adrenal gland provided much information concerning the factors involved but ten years of research had not been sufficient to evolve a method of treatment for all patients who suffered from Addison's disease.

A partial answer was contributed by the fourth stage of the investigation. Between 1930 and 1938 chemical investigation of the secretion of the adrenal cortex afforded a group of 28 crystalline compounds[11] and, moreover, in the mother liquor from which these were separated there was present at least one other compound which was not separated in crystalline form but whose presence could be demonstrated in a con-

vincing manner. This compound conferred on the body the power to retain sodium and to excrete potassium.[12]

Stage four is characterized by the preparation and use of a compound closely related in structure to the crystalline compounds that had been separated but when it was given to patients who had Addison's disease it behaved like the non-crystalline fraction, that is, it influenced the retention of sodium and the excretion of potassium.[13] The name of this compound is desoxycorticosterone.[11] In chemical structure it is the simplest member of the family of compounds present in the adrenal cortex. Although this compound produces a marked effect on mineral metabolism, it is safe to conclude that desoxycorticosterone is not present in any significant or useful amount in the secretion of the adrenal cortex. The metabolism of sodium, potassium and chloride is modified by an agent which in some ways is like desoxycorticosterone but which certainly is not this compound.

After desoxycorticosterone became available there were high hopes that it would restore patients who had Addison's disease to a normal state of health. Many patients were returned to a more useful life but even so they did not enjoy a sense of strength or well-being and some patients died although the concentration of sodium, potassium and chloride in the blood were within normal limits. It became clear that something more was required and beginning in 1940 attention was turned to the large-scale production of some of the crystalline compounds which had been separated and to which chemical structures had been assigned.

All 28 compounds isolated from the gland belong to the same family of organic substances—the steroids.[11] Steroids are found in all forms of animal life and in plants, insects and microorganisms such as yeast, but the members of the steroid family that are so abundant in the adrenal cortex are not found anywhere else. The compounds separated from the adrenal cortex all have the same arrangement of atoms of carbon in the molecule and one differs from another only in the position and form of attachment of from three to five atoms of oxygen and also the number of atoms of hydrogen. Preparation of these compounds on a large scale from starting material more abundant than the adrenal cortex was carried out during stage five, and this part of the investigation was notable for the rich reward which came when one of the bile acids was converted into cortisone. This was accomplished in 1948.[14, 15]

When this major contribution of the chemist was placed at the disposal of the physician, research in medicine went forward at a quickened pace. It was first shown that patients who had Addison's disease were restored to an almost normal condition by a small amount of cortisone and a few milligrams of desoxycorticosterone given daily. Under this regimen these patients enjoyed a sense of well-being, they could endure physical and psychic strain and could return to their usual active life.

The ability to control the symptoms of Addison's disease furnished evidence that at least one objective of the investigation had been attained and this would have been a generous reward for the time and effort which had been required but it was soon shown that cortisone could be used in a much wider field. Cortisone was found to influence more than twenty-five different clinical syndromes.

These dramatic events crowded with human interest are now taking place in stage six of the study of the adrenal cortex. The scope of the investigation has suddenly widened and human concern has been aroused. No radio announcer was present when the first few patients who had Addison's disease were treated with salt or with an extract of the adrenal cortex, but now some item of interest concerning the adrenal cortex is to be found almost daily in newspapers or popular magazines.

In retrospect it can now be seen that the elucidation of the chemical nature of the hormones of the adrenal cortex was made possible by previous work on the structure of steroids. The fundamental research which had been carried out on the chemical structure of cholesterol, the bile acids and sex hormones came to fruition between 1932 and 1934. This work just preceded the isolation of the crystalline compounds from the adrenal cortex. When these compounds were separated as single substances, each in a high state of purity, it became a relatively simple matter to determine their chemical structure, for they were all members of the steroid family. The finger of opportunity pointed strongly in the direction of preparation of these compounds on a large scale so that they would be available for use in clinical medicine. This part of the work, which has been carried out by many investigators in the field of organic chemistry, is a magnificent contribution to our knowledge of the chemistry of the steroids. The outstanding results—the preparation of cholesterol, cortisone and hydro-

cortisone by total synthesis—will always remain as landmarks of organic chemistry.[16]

A survey of the record of the physiological investigation also is instructive. The influence of sodium, potassium and chloride on physiologic processes, the effect of desoxycorticosterone on these same ions and the relative failure of cortisone and hydrocortisone to influence the metabolism of these ions were results which were recognized during the early stages of the work. The dramatic results afforded by cortisone and hydrocortisone on many diseases appeared to be sharply separated from the former experience with desoxycorticosterone. The clinical response was quite new and could not have been predicted from anything that was known.

Now, however, the time has come to relate the physiologic activity of the secretion of the adrenal cortex to the compounds separated from the gland. When this is done it becomes apparent that cortisone and hydrocortisone cannot be regarded as *the* only hormones of the adrenal cortex. Neither of these compounds confers on the patient who has Addison's disease the power to retain sodium and chloride and to excrete potassium unless it is administered in large amounts. It is necessary to postulate that the secretion of the adrenal cortex contains another unknown agent which has a marked effect on mineral metabolism.

This hypothesis is based on a firm foundation for it can be shown that the material which remains after separation of the crystalline compounds can function in this manner. The investigation of the adrenal cortex has now passed into stage seven which involves the identification of this important agent.

Interest in the control of mineral metabolism has been suppressed because of the excellent clinical results achieved with desoxycorticosterone. This steroid became available in 1938 and since that time the treatment of patients who had Addison's disease has been quite satisfactory in so far as mineral metabolism is concerned. For this reason the hormone in the adrenal cortex which performs this same function has not attracted much attention. Indeed some investigators have believed that mineral metabolism was controlled by small amounts of desoxycorticosterone. Others have thought that corticosterone or some other known steroid was the effective agent.

In any event the identity of the hormone did not appear to be of first importance and attention was turned toward the 11-oxygenated

steroids because no substitute for their action was known. Now that cortisone and hydrocortisone have been made available the investigation of the hormone which controls mineral metabolism can be viewed from a new perspective. The immediate question to be answered is whether the physiologic activity of this agent is limited to the distribution and excretion of electrolytes or does it have other important effects.

If cortisone and hydrocortisone modify organic metabolism and another quite different hormone influences mineral metabolism, and if these several hormones are all delivered as essential constituents of the secretion of the adrenal cortex, how is it that they appear to be released in amounts which are the most satisfactory? There are many possible explanations but the actual state of affairs cannot be determined by speculation. This problem, however, can be answered by further investigation.

Soon after publication of the results obtained by the use of cortisone in rheumatoid arthritis and other diseases two questions were asked by many investigators. One concerned the value of other compounds which would be as good as, or better than cortisone. The second question was how does cortisone produce its effects? The complete answer to the first question will come only after many more years of research, but today cortisone and closely related hydrocortisone (compound F) stand above and apart from all other compounds. The interest in pregnenalone and its derivatives, in desoxycorticosterone administered together with vitamin C, and in many other substances has subsided. It seems probable that the two hormones which have survived the rigid selection of nature throughout the development of animal life will continue to hold their place—perhaps they never will be equaled.

During the past three years Merck and Company, Inc. have performed a miracle in making cortisone and hydrocortisone available. They have found answers to most difficult problems and they have produced cortisone in such volume that the price today is only 5 per cent of the price in 1949. At that time the high cost of the hormone was a stimulus in the search for something else which would be just as good. Now that stimulus has disappeared.

As to how cortisone and hydrocortisone influence the body in health and in disease we know very little more than we did in 1948. It has been shown that these hormones modify the metabolism of protein,

carbohydrate and fat, as well as that of sodium, potassium and calcium. Somewhere within the results already at hand the evidence of how they function may be hidden, but if so, it is well hidden.

Much has been discovered about the nature of some of the diseases influenced by cortisone. Some syndromes may involve a relative deficiency of the hormones of the adrenal cortex since they are relieved by moderate doses of the hormones but it now seems improbable that all of the conditions which respond to treatment with cortisone are caused simply by a lack of cortisone. Much more work will be required to explain the etiology of rheumatoid arthritis, lupus erythematosus, pemphigus, asthma and hypersensitive states.

Periarteritis nodosa, frequently a fatal disease, has been treated successfully with cortisone but to assume that this condition is caused by a lack of the hormone seems unwise. It is also unlikely that a disturbance in the relative amounts of the different hormones in the secretion of the adrenal cortex can be an important etiologic factor.

One of the less obvious results associated with the availability of cortisone was the realization of the complexity of the problems concerned with its action.

During the past three years cortisone has been administered on a large scale as a therapeutic agent. Some patients have well tolerated clinically effective doses of cortisone and hydrocortisone and have responded in a most satisfactory manner. In others the continued use of large or moderately large daily doses has produced hypercortisonism in varying degree.

Treatment of patients with the hormones of the adrenal cortex requires study of each individual case, for the daily dose depends on many variables. This demands the close attention of the physician. In this respect cortisone and hydrocortisone are similar to insulin.

I have described seven stages of the investigation of the hormones of the adrenal cortex. The sixth stage, the study of the effect of cortisone and hydrocortisone in clinical medicine, is still under investigation and evidently will continue for some time to come. New uses for these hormones are still being reported and as experience is gained the full value of these new therapeutic agents will be afforded.

At the moment, stage seven, investigation of the chemical nature of the agent which modifies mineral metabolism, is slowly gathering momentum. When this problem has been solved it will be possible to

answer many questions which have accumulated throughout the past twenty years.

To answer these questions and to study the physiologic effects of the new agent will require stage eight. It can be seen that for both physiologist and clinician stage eight will be an important one. I shall not assume the role of a prophet but the future historian may say that a clear understanding of the hormones of the adrenal cortex was not possible until stage eight had been reached.

But that will not be the end, for after the chemical nature of the hormones of the adrenal cortex is known then still another chapter must be written which will concern the interrelation and integration of these hormones with those of the other endocrine glands. That will require stage nine.

It does not seem profitable to schedule future results beyond this. By the time stage nine has been passed it may then be said that nature did not reveal her secrets in a moment. Even then we shall not be certain that the innermost sanctuary has been explored.

REFERENCES

1. Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. F. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions, *Arch. intern. Med. 85*:545-666, 1950.
2. Addison, T. *On the constitutional and local effects of disease of the suprarenal capsules.* London, S. Highley, 1855.
3. Best, C. H. and Taylor, N. B. *The physiological basis of medical practice.* 3.ed. Baltimore, Williams & Wilkins, 1940.
4. Hartman, F. A. and Brownell, K. A. The hormone of the adrenal gland, *Science 72*:76, 1930.
5. Swingle, W. W. and Pfiffner, J. J. Revival of comatose adrenalectomized cats with an extract of the suprarenal cortex, *Science 72*:75-76, 1930.
6. Smith, A. H. and Smith, P. K. Inorganic salts in nutrition; electrolyte balance in the serum of rats receiving a diet deficient in inorganic constituents, *J. biol. Chem. 107*:681-88, 1934.
7. Baumann, E. J. and Kurland, S. Changes in the inorganic constituents of blood in suprarenalectomized cats and rabbits, *J. biol. Chem. 71*:281-302, 1927.
8. Loeb, R. F. Chemical changes in the blood in Addison's disease, *Science 76*: 420-21, 1932.
9. Allers, W. D., Nilson, H. W. and Kendall, E. C. Studies on adrenalectomized dogs; toxic action of potassium, *Proc. Mayo Clin. 11*:283-88, 1936.
10. Wilder, R. M., Kendall, E. C., Snell, A. M., Kepler, E. J., Rynearson, E. H. and Adams, M. Intake of potassium, an important consideration in Addison's disease, *Arch. intern. Med. 59*:367-93, 1937.
11. Reichstein, T. and Shoppee, C. W. Hormones of the adrenal cortex, *Vitamins & Hormones 1*:345-413, 1943.
12. Kendall, E. C. The influence of the adrenal cortex on the metabolism of water and electrolytes, *Vitamins & Hormones 6*:277-327, 1948.
13. Thorn, G. W., Howard, R. P., Emerson, K., Jr. and Firor, W. M. Treatment of

Addison's disease with pellets of crystalline adrenal cortical hormone (synthetic desoxy-corticosterone acetate) implanted subcutaneously, *Bull. Johns Hopkins Hosp. 64*:339-65, 1939.

14. Kendall, E. C. *The development of cortisone as a therapeutic agent. (Les prix Nobel)*, Stockholm, P. A. Norstedt und Söner, 1951.

15. Sarett, L. E. New method for the preparation of 17 (α)-hydroxy-20-ketopregnanes, *J. Amer. chem. Soc. 70*:1454-58, 1948.

16. Woodward, R. B., Sondheimer, F., Taub, D., Hensler, K. and McLamore, W. M. The total synthesis of steroids, *J. Amer. chem. Soc. 74*:4223-31, 1952.

MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

AT THE ACADEMY—4:30 P.M.

FRIDAY, FEBRUARY 6, 1953

Subject: DISORDERS OF THE BLOOD

Moderator: Claude E. Forkner—Associate Professor of Clinical Medicine, Cornell University Medical College; Attending Physician, New York Hospital

Members: Lloyd F. Craver—Professor of Clinical Medicine, Cornell University Medical College; Attending Physician, Memorial Center for Cancer and Allied Diseases

Joseph H. Burchenal—Attending Physician Chemotherapy Service, Memorial Hospital; Professor of Medicine, Sloan-Kettering Division of Cornell University Medical College

Paul Reznikoff—Professor of Clinical Medicine, Cornell University Medical College; Attending Physician, New York Hospital

Nathan Rosenthal—Consulting Hematologist, Mount Sinai Hospital; Formerly Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University

FRIDAY, MARCH 6, 1953

Subject: THE FAILING HEART

Moderator: Charles E. Kossmann—Associate Professor of Medicine, New York University College of Medicine; Visiting Physician, Bellevue Hospital

Members: Robert C. Batterman—Assistant Professor of Medicine, New York Medical College; Attending Cardiologist, Veterans Hospital, Bronx, N. Y.

Cary Eggleston—Consulting Physician, New York Hospital; Associate Professor of Clinical Medicine, Cornell University Medical College

Ludwig W. Eichna—Associate Professor of Medicine, New York University College of Medicine; Visiting Physician in Medicine, Bellevue Hospital

Charles K. Friedberg—Associate Attending Physician, Mount Sinai Hospital; Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University

Harold J. Stewart—Associate Professor of Medicine, Cornell University Medical College; Attending Physician, New York Hospital

FRIDAY, APRIL 3, 1953

Subject: RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

Moderator: Charles Ragan—Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University

DIAGNOSIS OF ENDOCRINE DISEASE: CLINICAL AND LABORATORY CONSIDERATIONS*

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THE subject of this evening's lecture is a broad one and the time allotted is hardly adequate to cover it with any reasonable degree of thoroughness. In view of this limitation it might perhaps be more desirable to confine ourselves to certain aspects of the problem, notably those phases dealing with adrenal and, to a lesser extent, adenohypophysial and thyroid function. In a general sense this evening's presentation will serve as a brief introduction to topics which will be discussed in much greater detail by other speakers during the course of this Fortnight.

The past two decades have witnessed broad and basic advances in the field of endocrinology. Newer and more precise techniques have been developed for the diagnosis of endocrine disease. The recognition and identification of glandular disturbances is less a matter of chance today and much more based on sound laboratory procedures than it was a quarter of a century ago. The problems of endocrinology have been considerably complicated by the fact that the concept of the field has expanded considerably. Where at one time we thought of endocrinology as a field concerned specifically with orthodox glandular abnormalities we now recognize that the glands of internal secretion play a significant role in all physiological processes and color and influence the manifestations of disease not heretofore considered endocrinological in character. With the elaboration of the concept of stress and the advent of corticotropin and various adrenal cortical fractions we have been provided with tools which are gaining us a progressively greater insight into homeostatic mechanisms and body response to disease.

We can perhaps best approach the general problem by a brief con-

* Presented at the 25th Graduate Fortnight of The New York Academy of Medicine, October 7, 1952.

sideration of the metabolic and biochemical effects of corticotropin in the intact animal. The stimulation of the adrenal cortex with corticotropin results in: 1) an increase in the urinary excretion of the neutral 17-ketosteroids and the 11-oxygenated steroids; 2) an increase in the peripheral total white blood cell count, due mostly to an increase in the absolute number and percentage of neutrophilic granulocytes; 3) a decrease in the small normal lymphocytes and a virtual disappearance of the eosinophiles; 4) variable changes in water and electrolyte metabolism. Increased adrenal cortical function is often associated with a retention of water, a decrease in the urinary excretion of sodium, an increase in the serum sodium level, a decrease in the serum potassium and chlorides, and an increase in the urinary excretion of these ions. The increased urinary loss of chlorides may result in the development of a hypochloremic alkalosis which is more readily correctible by the administration of a potassium salt in addition to ammonium chloride than where this latter compound is employed alone. Such changes in water and electrolyte metabolism, however, by no means always occur. Increased adrenal cortical function may not be associated with any overt alterations in water and electrolyte balance, or it may be characterized actually by a water diuresis with an increased urinary loss of sodium. In some instances stimulation of the adrenal cortex results in an expansion of the extracellular space as measured by inulin.[1] This increase in extracellular fluid volume is associated with an increase in the glomerular filtration rate, relatively little change in the renal plasma flow, and a progressive increase in the renal filtration fraction. These phenomena reach a peak on the eighth to tenth day and are then followed by a urinary diuresis of water, sodium, and, to a lesser extent, of potassium, even though treatment with corticotropin is continued.

Increased adrenal cortical function is characterized by still other changes. There may occur significant alterations in carbohydrate and protein metabolism and changes in the metabolism of calcium and phosphorus. With hypercorticalism there occurs a decrease in the absorption of calcium and phosphorus from the intestinal tract and an increase in the fecal excretion of the former ion and, to a lesser extent, of the latter. That this is not an expression simply of decreased absorption of these ions is evidenced by the fact that the total calcium excretion is considerably in excess of the intake.[2] For the formation of bone, calcium is deposited in a bony matrix which is essentially protein in

character. With increased adrenal cortical function there occurs a decrease in the protein body mass including that of the bony matrix, so that the deposition of calcium for the formation of bone is interfered with. The reduction in protein mass in adrenal cortical hyperfunction is due to an interference with the build-up of amino acids for the formation of protein, the so-called "antianabolic" effect, and perhaps to an increase in the breakdown of proteins, the "catabolic" effect. The interference with the buildup of proteins from amino acids and the increased formation of amino acids from the excessive catabolism of proteins permits the diversion of the accumulated amino acids for gluconeogenesis. Carbohydrate metabolism is further interfered with in that certain adrenal cortical fractions inhibit the peripheral utilization of glucose. In view of these findings the hypoglycemia of Addison's disease and the hyperglycemia and glycosuria of Cushing's syndrome become understandable.

With these general observations as a background, let us examine some of the clinical manifestations and laboratory means available to us for the recognition of adrenal cortical disease.

Adrenal Cortical Hyperfunction

When we speak of adrenal cortical hyperfunction we must bear in mind two different sets of signs and symptoms: 1) those associated with sexual abnormalities, which we refer to as the adrenogenital or virilizing syndrome, characterized by hirsutism, amenorrhea, enlargement of the clitoris, decrease in size of the breasts, female pseudohermaphroditism, etc.; and 2) metabolic abnormalities characterized by purplish striae, obesity, rounding of the facies, hypertension, osteoporosis, and disturbance in carbohydrate metabolism. The latter group of signs and symptoms is referred to as Cushing's syndrome. Most patients with adrenal cortical hyperfunction present a combination of both groups, but in some cases one may be present to the exclusion of the other, or one may be preponderantly present. There is a difference in prognosis between the two groups of patients which should be remembered. Patients with the adrenogenital syndrome alone, due to adrenal cortical tumor or hyperplasia, constitute a good operative risk. When patients have evidence of Cushing's syndrome, however, the removal of an adrenal tumor is associated with a considerable operative risk, since the contralateral adrenal is usually atrophic, and following the operation

these patients often develop a severe and curious shock not readily responsive to the usual forms of therapy. The pure adrenogenital syndrome of adrenal origin is always associated with either adrenal cortical hyperplasia or tumor. Cushing's syndrome, however, may be due to a pituitary basophilic adenoma or an adrenal cortical tumor or hyperplasia. In any event, both syndromes are the result of increased adrenal cortical function.

Increased adrenal cortical function should theoretically be characterized by: 1) increase in serum sodium, reduction in serum potassium and chloride; 2) development of a hypochloremic, hypopotassemic alkalosis; 3) increase in the urinary excretion of the neutral 17-ketosteroids and 11-oxygenated steroids. Actually, in only half of the patients with pathologically proven adrenal cortical tumor or hyperplasia with a characteristic clinical picture is there any change in the blood electrolytes. So that a perfectly normal electrolyte pattern does not mitigate against the diagnosis, while a considerable elevation of the serum sodium level and the development of a hypochloremic, hypopotassemic alkalosis is strongly suggestive of the diagnosis. It is perhaps interesting to mention that prolonged treatment with cortisone or ACTH will often induce precisely these electrolyte changes. The urinary excretion of the neutral 17-ketosteroids is generally increased in patients with the adrenogenital syndrome, particularly in those instances associated with bilateral adrenal cortical hyperplasia or malignant tumor. The 11-oxygenated steroids in patients with a preponderant or pure virilizing syndrome may or may not be increased slightly but are generally normal. In patients with a preponderant Cushing's syndrome the urinary excretion of the neutral 17-ketosteroids is generally within the normal range or only slightly elevated in instances due to pituitary basophilism or in instances of a benign adrenal cortical tumor. The urinary excretion of the 11-oxygenated steroids is usually, but not always, increased in this group of patients. When the syndrome is due to a malignant tumor, the urinary excretion of both fractions is as a rule considerably elevated. In summary, then, a markedly elevated excretion of the neutral 17-ketosteroids favors the diagnosis of a hormone-producing adrenal cortical carcinoma, be the clinical picture that of virilism, Cushing's syndrome, or both. In adrenal cortical hyperplasia with virilism, such as occurs in female pseudohermaphroditism or virilism associated with a benign adrenal cortical tumor, the urinary excretion of the neutral 17-

ketosteroids is usually considerably increased. Cushing's syndrome due to pituitary basophilism or benign adrenal cortical tumor is frequently associated with no or slight increase in the excretion of the neutral 17-ketosteroids and some increase in the urinary 11-oxygenated steroids.

It is sometimes possible to distinguish between adrenal cortical tumor and hyperplasia in virilism by determining the influence of cortisone on the urinary excretion of the neutral 17-ketosteroids. In those instances of virilism associated with an increase in the urinary excretion of these fractions the daily administration of 100 mgm. of cortisone for several days will result in a reduction in the urinary 17-ketosteroids in instances due to bilateral adrenal cortical hyperplasia, but no change in those cases where the syndrome is due to tumor.[3]

Finally, patients with adrenal cortical hyperfunction may show a paradoxical response to the injection of desoxycorticosterone acetate. The injection of desoxycorticosterone into normal individuals or patients with Addison's disease is associated with a retention of fluid and a decrease in the urinary excretion of sodium. In patients with adrenal cortical hyperfunction, however, the injection of this fraction under test conditions is often associated with an increase in the urinary excretion of both sodium and chloride.[4]

It must be emphasized that all of these tests are much more significant when they are positive and of much more questionable value when they are negative.

Adrenal Cortical Hypofunction

Aside from the clinical picture of Addison's disease, which is rather characteristic and evidenced by profound asthenia, weight loss, pigmentation, hypotension, anorexia, nausea and vomiting, constipation or diarrhea, and episodes of crisis, the following laboratory procedures are of great help in establishing the diagnosis: 1) *Determination of the blood electrolytes.* During the interim period, that is the period when the patient is not in crisis, there may or may not be a reduction in the serum sodium and chloride levels and a modest elevation in the serum potassium. When the patient presents the classical clinical picture of Addison's disease and this is associated with a significant reduction in serum sodium to less than 135 meq/l, the diagnosis of Addison's disease may be considered well established. A normal serum sodium, however, does not exclude the diagnosis. 2) *Salt deprivation test.*[5] When a normal

individual is placed on a salt free diet there promptly occurs a proportionate decrease in the urinary excretion of sodium, and such individuals may continue on a sodium restricted diet for an indefinitely prolonged period of time without any undue ill effects. Witness the patients with hypertension who are maintained on rice diets, such diets being exceedingly low in sodium, averaging 7 to 8 meq/Na daily. The patients with Addison's disease, however, behave quite differently. The illness is characterized by a constant excessive urinary loss of sodium. When such patients are placed on a salt free diet they continue to lose sodium in the urine and with it water, so that they are in negative sodium and water balance. The patient with Addison's disease when placed on a restricted sodium intake will be precipitated into adrenal crisis within two to six days. In performing this test, however, one must not prolong it to the point where the patient develops overt clinical evidences of acute adrenal cortical insufficiency. A reduction in the serum sodium and chloride levels, an increase in the hematocrit suggesting dehydration and hemoconcentration, an increase in the blood urea nitrogen, and a significant reduction in blood pressure are all evidences of impaired adrenal cortical function, constitute a positive test, and occur before more significant clinical signs of adrenal insufficiency occur. When a laboratory is not available for the determination of serum sodium or chloride the changes outlined above in the blood pressure, urea nitrogen, and hematocrit are ample.

A positive response to the salt deprivation test is indisputable evidence of marked impairment of adrenal cortical function, and the absence of such a response in a suspected patient renders the diagnosis untenable. However, the test is not without hazard and should be performed in a hospital under careful observation and with intravenous saline and adrenal cortical extract available for immediate use if necessary. This test should not be employed unless other tests, much safer to the patient but perhaps less specific, yield equivocal results.

3) *Eosinophile response to stimulation with ACTH.* In the normal individual stimulation of the adrenals with a test dose of 25 mgm. of ACTH results in a marked reduction of the absolute number of eosinophiles within a four hour period. In patients with Addison's disease a reduction generally does not occur, or is less than 50 per cent. This test is a satisfactory, but not always reliable, test of adrenal cortical hypofunction. In the normal individual adrenal stimulation with ACTH

at six hour intervals for a twenty-four or forty-eight hour period results in a considerable increase in the urinary excretion of the neutral 17-ketosteroids and the 11-oxygenated compounds. In patients with Addison's disease this response does not occur. Since in the male the 17-ketosteroids are elaborated in major part by the adrenals and one-third by the testes, and the 11-oxygenated steroids entirely by the adrenals, these fractions are markedly reduced in patients with Addison's disease and fail to increase with stimulation with ACTH. 4) *Water loading test.*[6, 7] This test is based upon the fact that patients with Addison's disease fail to develop an adequate diuresis within a given period of time following the oral ingestion of large quantities of water. The original test has been modified so that the patient is given 1500 cc. of water to drink over a forty minute period and all the urine voided during the next five hours collected and the volume measured. In individuals with intact adrenals the total urinary voiding will generally exceed 1200 cc., while that of patients with Addison's disease will measure less than 800 cc. The two major pitfalls in the use of this test are concerned with the presence of renal or hepatic disease where similar reductions in urine volume may be obtained. In patients suspected of having Addison's disease on the basis of this procedure, the test may be further sharpened by observing the effect on the water diuresis by the administration of cortisone. In such patients the urine volume may be considerably enhanced following the oral administration of 50 mgm. of cortisone two to four hours prior to the ingestion of the 1500 cc. of water.

The discussion thus far has centered around the recognition of orthodox adrenal cortical disease. But, as indicated earlier in this lecture, these glands play a significant role in the response of the body to a large variety of stressing situations and disease processes. We can perhaps best examine this relationship by applying the phenomenon of stress to clinical surgical problems.

When an experimental animal or human is subjected to stress one of the mechanisms of response involves the discharge of epinephrine from the adrenal medulla. The epinephrine, either directly or perhaps through the hypothalamus, stimulates the adenohypophysis to the elaboration of corticotropin and thyrotropin, and perhaps other hormonal fractions. The corticotropin then stimulates the adrenal cortex to the secretion of its steroid hormones, while the thyrotropin acts

similarly on the thyroid gland. This, in brief and rather considerably simplified form, is the essence of the homeostatic response to stress. When a patient is subjected to a surgical procedure, an acute medical illness, or an emotional experience, this general phenomenon comes into play. Following surgery there occurs a prompt and marked decrease of the circulating eosinophiles and an increase in the urinary excretion of nitrogen.[8] In addition, there occurs a transient increase in the urinary excretion of the neutral 17-ketosteroids and a more prolonged increase in the excretion of the 11-oxygenated compounds.[9] At the same time there occurs a decrease in the sodium and chloride content of sweat,[10] a reduction in the serum chloride and potassium levels, and often an elevation in the CO_2 content.[11]

These phenomena are recognizable as identical with similar changes which occur following the administration of corticotropin. It would appear reasonable, therefore, to assume that the act of surgery evokes a temporary hyperadrenocorticalism which is important for the adequate response of the patient to the surgical procedure. It is possible and desirable to determine the integrity of this mechanism before the patient is subjected to anesthesia and surgery. The effect of corticotropin on the peripheral eosinophile count and the water loading test provide two simple methods for assaying the status of the adrenals. Where the response to these tests is inadequate, such a patient constitutes a poor operative hazard unless he is adequately prepared before operation with the necessary adrenal cortical fractions and treated postoperatively with the steroids for a suitable period of time.

Adrenal Medullary Hyperfunction: Pheochromocytoma

The clinical manifestations resulting from a pheochromocytoma are similar to those produced following the injection of a good sized dose of epinephrine. Indeed, the attacks are due to the sudden liberation of excessive amounts of epinephrine and norepinephrine from chromophilic tissue. The disease is characterized by paroxysmal episodes of hypertension, cardiac palpitation, throbbing in the head, headache, nausea and vomiting, and, in half the patients, glycosuria. Not infrequently the hypertension is permanent in character. The tests for pheochromocytoma are based on two principles: First, to attempt to induce an attack through (a) vigorous massage of the abdomen, (b) intravenous injection of 0.05 mg. of histamine base, and (c) the in-

travenous injection of 200 to 300 mgm. of tetraethylammonium chloride. In the presence of a pheochromocytoma, the latter two will each cause a marked rise in the systolic and diastolic blood pressure within three to five minutes and a duplication of an attack. The advantage of the tetraethylammonium chloride lies in the fact that an induced attack can be promptly controlled by placing the patient in the upright position. Other agents such as mecholyl and insulin, starvation, etc., have also been used to induce attacks, although with only modest success. The second principle of diagnosis is to determine whether a particular episode of hypertension is due to the discharge of adrenalin and can, therefore, be reduced by the use of adrenolytic agents. Such substances are benzodioxane, which is used in a dosage of 10 to 15 mgm. intravenously, and regitine, 2 to 4 mgm. given intravenously. In the presence of hypertension due to the discharge of epinephrine, both chemicals will produce a marked drop in both the systolic and diastolic pressure within one-half to three minutes. The interpretation of these results is significant only if the changes in blood pressure are marked. The effect of regitine is further conditioned by the presence of renal damage with azotemia. Under such circumstances this agent will cause a reduction in blood pressure in the absence of a pheochromocytoma.

The Laboratory Recognition of Pituitary Disturbances

Extensive destruction of the adenohypophysis is characterized by a typical clinical picture, referred to as Simmonds' cachexia or, more lately, Sheehan's syndrome. The latter applies essentially to those instances of adenohypophysial destruction which occur secondary to a postpartum hemorrhage. In the presence of such extensive destruction there are both clinical and laboratory evidences of involvement of the other endocrine glands, particularly the adrenals, gonads, and thyroid. The difficulty arises in the recognition of more circumscribed and limited adenohypophysial disease. The presence of overactivity of the pituitary can be recognized more readily in association with the proper clinical picture, rather than by laboratory tests. We know that the clinical picture of acromegaly is due to excessive hormonal secretion of the eosinophilic cells of the pituitary. The associated evidences of hyperthyroidism or disturbances in carbohydrate metabolism, although in the presence of acromegaly, have their origin in the disturbed function of the adenohypophysis, and by themselves are not pathognomonic

of pituitary disease. Similarly, in Cushing's syndrome we can suspect the pituitary origin of the illness only if we are certain as to the absence of an adrenal tumor. So that, in a broad sense, we can suspect the presence of pituitary disease where we can demonstrate a simultaneous disturbance of function of several endocrine glands, either by clinical or laboratory methods. In this regard, then, a low basal metabolic rate with a decrease in uptake of radioactive iodine, occurring along with a significant decrease in the urinary excretion of the 17-ketosteroids and the 11-oxygenated steroids, and a reduction or absence of urinary gonadotropin, suggests the diagnosis of impaired adenohypophysial function.

The major difficulty in diagnosis arises in the differentiation between primary and pituitary myxedema, and their differentiation is based upon the following features: 1) the clinical and laboratory response to exogenous thyrotropin; 2) clinical and laboratory evidence of involvement of the other endocrine glands; 3) insulin and insulin-glucose tolerance tests; and 4) exophthalmometric readings. In patients with hypothyroidism due to injury or destruction of the adenohypophysis, the parenteral administration of thyrotropin in a daily dosage of 10 to 20 mgm. is followed by an increase in the serum protein-bound iodine. These laboratory changes are associated with improvement in the clinical picture. In the patient with primary myxedema, however, none of these changes is to be expected. This method may also serve to detect those instances of selective failure of thyrotropin secretion not associated with failure of other endocrine glands. The administration of thyrotropin or thyroid extract to patients with pituitary myxedema, however, is fraught with some hazard. The increased metabolic needs attendant upon the use of these agents may exceed the ability of the adrenal cortex to supply sufficient adrenocortical hormones and thus precipitate adrenal insufficiency. Thus, its use in patients with Sheehan's syndrome must be approached cautiously. We can get some inkling of approaching adrenal exhaustion on the basis of certain laboratory observations. In some studies conducted in our laboratory we found that the administration of thyrotropin to patients with adenohypophysial destruction was followed by a progressive decrease in the urinary excretion of the 11-oxygenated steroids which were already low to begin with. Their total disappearance from the urine was promptly followed by the development of adrenal crisis. On the other hand, the urinary

excretion of the neutral 17-ketosteroids remained unaffected. This may be contrasted with the results observed in patients with thyroidal myxedema in which the urinary excretion of these compounds remained unaffected despite prolonged treatment with thyrotropin. This does not mean that adrenal insufficiency may not occur in patients with primary myxedema. Indeed, such instances have been reported, but, in contrast to the situation which prevails in patients with pituitary myxedema, adequate therapy with desiccated thyroid extract resulted in a marked improvement of adrenal cortical function.

Blood and urine assays for thyrotropin would theoretically furnish an excellent means of distinguishing between primary and secondary myxedema. In the former, since there is a marked increase in the pituitary secretion of this fraction, it would be reflected in its increase in both the blood and the urine, while the latter would be characterized by its decreased secretion and, therefore, either reduction or complete absence from the blood and urine. Unfortunately, the procedures which are at present available for its identification are unsatisfactory. We are engaged in the measurement of the urinary excretion of this pituitary fraction employing the uptake of I^{131} by the thyroid of the young guinea pig. Preliminary evidence would indicate that, as we suspect on experimental grounds, there is an increase in the urinary excretion of a thyroid stimulating fraction in patients with primary hypothyroidism.

We can sometimes utilize exophthalmometric measurements to distinguish between primary and secondary myxedema. Exophthalmos may perhaps be attributed to the effects of some adenohypophysial fraction on the retro-orbital tissue. It is by no means certain that this fraction is thyrotropin. There is considerable evidence to suggest that some other fraction in addition to thyrotropin is essential for the production of this phenomenon. In any event, it would be expected that in patients with primary myxedema, where the pituitary secretes excessive quantities of these fractions, the degree of exophthalmos would in general exceed that encountered in patients with pituitary insufficiency. However, since the range of exophthalmometric readings in normal subjects is wide, it is not surprising that the readings found in patients with primary myxedema frequently fall within the normal range, although not infrequently definite exophthalmic measurements are observed. In such patients, the exophthalmometric readings decrease

following treatment of the myxedema with thyroid extract. The data available in patients with hypopituitarism are scant, but the values, including those reported from our laboratory, are well within the normal limits. Normal exophthalmometric measurements may not be used as evidence for or against primary or secondary myxedema. However, the association of exophthalmos with hypothyroidism would suggest primary thyroid disease.

As mentioned previously, when hypothyroidism is associated with laboratory evidence of impairment of function of the other endocrine glands, the presence of primary pituitary disease must be strongly suspected. Means and his associates pointed out that hypothyroidism associated with a low urinary gonadotropin titer in the presence of amenorrhea would suggest the pituitary origin of the myxedema. A normal or elevated titer is more commonly encountered in primary myxedema. The distinction on the basis of the urinary gonadotropin excretion is by no means absolute. Reduced urinary gonadotropin titers have been reported in primary myxedema, but, interestingly enough, in the latter group of patients the administration of desiccated thyroid extract results in an increase in the urinary excretion of gonadotropin, occurring concomitantly with improvement in the clinical picture.

The response to insulin is a useful adjuvant in the diagnosis of deficient pituitary function. In this test we are not so much concerned with the degree of reduction of the blood sugar level as we are with the period of time that elapses until the blood sugar returns to a normal level. This phenomenon is referred to as "hypoglycemia unresponsiveness." When 3 to 5 units of insulin are parenterally administered to a normal individual there may occur a drop in the blood sugar to hypoglycemic levels, which attains its lowest point within twenty to thirty minutes and returns to normal levels within one and one-half to two hours. In patients with true hypopituitarism, the drop in the blood sugar level following the administration of insulin may or may not be as marked as that observed in normal individuals but its return to normal levels is delayed, generally beyond the two hour period. It is this point, rather than the extent of the drop, which is significant. The patient with primary myxedema behaves in still another fashion. Here there is a delay in the reduction of the blood sugar level, so that the lowest point may not be reached for forty-five minutes, while the return to pretreatment level may or may not be prolonged. When the

combined insulin-glucose tolerance test is employed, the test is further sharpened in that the "hypoglycemia unresponsiveness" of the patient with hypopituitarism is easily demonstrated, while the curve which is obtained in the patient with primary myxedema resembles that of the normal subject.

In the final analysis, there is no one procedure which distinguishes amongst the various conflicting endocrine states. It requires the intelligent correlation of clinical judgment and laboratory observations to arrive at the correct conclusion. Often simple procedures can serve our purposes adequately. In a patient with myxedema we can sometimes establish the primary character of the disease by passing a Geiger counter over the neck and upper chest following the administration of a tracer dose of radioactive iodine. If no uptake occurs, this is good presumptive evidence that such a patient has congenital absence of the thyroid and, therefore, has primary myxedema. In such instances elaborate laboratory procedures are not required to establish the precise diagnosis. Similarly, a careful history, an intelligent physical examination, x-ray studies of the sella demonstrating enlargement and erosion of the floor or clinoid processes will establish the correct diagnosis in many instances. Finally, it is important to remember that the interpretation of the multiple laboratory procedures that a patient may be subjected to is not always simple, nor are the results always clear-cut. Considerable overlapping of results occurs, and the findings can only serve as an adjuvant to careful clinical observation and study.

REFERENCES

1. Levitt, M. F. and Bader, M. E. Effect of cortisone and ACTH on fluid and electrolyte distribution in man, *Amer. J. Med. 11*:715-23, 1951.
2. Soffer, L. J., Gabrilove, J. L. and Jailer, J. W. Metabolic studies with adrenocorticotropin in Cushing's syndrome and in virilism, *J. clin. Endocrin. 10*:594-632, 1950.
3. Wilkins, L., Lewis, R. A., Klein, R. and Rosemberg, E. The suppression of androgen secretion by cortisone in a case of congenital adrenal hyperplasia; preliminary report, *Bull. Johns Hopkins Hosp. 86*:249-52, 1950.
4. Soffer, L. J., Gabrilove, J. L. and Jacobs, M. D. Salt tolerance test in normal individuals and in patients with adrenal cortical hyperfunction, *J. clin. Invest. 28*:1091-93, 1949.
5. Harrop, G. A., Weinstein, A., Soffer, L. J. and Trescher, J. H. Diagnosis and treatment of Addison's disease, *J. Amer. med. Assoc. 100*:1850-55, 1933.
6. Robinson, F. J., Power, M. H. and Kepler, E. J. Two new procedures to assist in recognition and exclusion of Addison's disease, *Proc. Mayo Clin. 16*:577-82, 1941.
7. Soffer, L. J. and Gabrilove, J. L. A simplified water-loading test for the diagnosis of Addison's disease, *Metabolism*

1:504-10, 1952.

8. Hardy, J. D. *Surgery and the endocrine system.* Phila., W. B. Saunders Co., 1952.
9. Kinnunen, O. Gynecological operations as stress — the excretion of the 17-ketosteroids as indicator, *Acta endocrin. 8*:385-92, 1951.
10. Johnson, H. T., Conn, J. W., Iob, V. and Coller, F. A. Postoperative salt retention and its relation to increased adrenal cortical function, *Ann. Surg. 132*:374-85, 1950.
11. Zimmermann, B. Endocrine mechanism concerned in postoperative electrolyte changes, *Surg. Forum* (*Proc. clin. Congr. Amer. Coll. Surgeons*) 1950: 447-56.

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EFFECTS OF SUBTOTAL ADRENALECTOMY ALONE AND COMBINED WITH SYMPATHECTOMY UPON THE BLOOD PRESSURE LEVELS AND COMPLICATIONS OF SEVERE ARTERIAL HYPERTENSION*

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PATIENTS with arterial hypertensive disease may exhibit periods of inexplicable spontaneous lowering of blood pressure, improvement of cardiac function or even regression of eye ground changes. The importance of recognizing that such spontaneous improvements can occur irrespective of coincidental treatment has frequently been stressed. However, as hypertensive disease advances and the all too familiar signs of an ominous prognosis begin to make their appearance, periods of spontaneous improvement are less commonly observed. The acid test of treatment is what it can accomplish at such stages of the disease.

Ever since hypotension was recognized as one of the cardinal features of Addison's disease, it has been realized that the adrenal gland must play some important part in the maintenance of normal blood pressure levels. When, however, the hypertensive patient develops Addison's disease, not only may the hypertension be abolished but the pressure may fall to hypotensive levels, much as it does in those with no previous hypertension. This behavior suggests that the adrenals may be concerned in some manner with activation of the blood pressure elevating mechanism of the hypertensive process. It should be stated, however, that in at least two reported cases, mild hypertension was found in Addison's disease associated with severe renal involvement.[1, 2] Thus, it appears that "renal hypertension" may persist in the absence

* Read in abstract at the Stated Meeting of The New York Academy of Medicine, February 7, 1952.
This manuscript was received for publication August 6, 1952.
From the Edward B. Robinette Foundation, Medical Clinic, and the Department of Surgery, School of Medicine and Hospital of the University of Pennsylvania.
This investigation was supported, in part, by research grants from the National Heart Institute, U. S. Public Health Service, Ciba Pharmaceutical Products, Inc., The Squibb Institute for Medical Research, Sandoz Pharmaceuticals, and Eli Lilly and Company.

of adrenal function despite Goldblatt's failure to produce hypertension in adrenalectomized animals by his renal ischemia method.[3] We know of no adequate basis for an opinion as to a relationship between abnormality of adrenal gland function and the etiology of arterial hypertension, save in the presence of certain adrenal or pituitary gland tumors. Despite negative results of efforts to incriminate the adrenals in the etiology of essential hypertension, the question cannot be regarded as settled at this time. For instance, the possibility exists that the development of methods which will permit differentiation of components of adrenal cortical secretion or their metabolic products upon a quantitative basis may throw light upon this problem.

The unfavorable clinical course of Addison's disease, and above all the dire consequences of acute adrenal insufficiency occasionally produced surgically by accident in the past were undoubtedly responsible for the avoidance of extensive adrenalectomy in the attempt to develop effective treatment of hypertension. As long ago as 1914, Crile[4] went so far as to perform unilateral adrenalectomy in an effort to control hypertension. DeCourcy in 1934[5] removed two thirds of each adrenal gland and in 1950 three-fourths.[6] Leriche[7] combined sympathectomy with unilateral adrenalectomy and Neuhof[8] combined sympathectomy with the removal of half of each adrenal gland. In 1949 and again in 1950, Green and his colleagues[9, 10] reported the results of almost total adrenalectomy in a young woman with severe arterial hypertension and diabetes. Convalescence was stormy and a great deal of adrenal cortical replacement therapy, mainly aqueous adrenal cortical extract, was employed in the early postoperative periods. Subsequently the blood pressure fell to normal levels, and the diabetes was greatly improved. At the time of the second report, it was stated that improvement had been maintained and the requirement for replacement therapy had diminished.

Our interest in the possibility of developing an operative procedure utilizing adrenalectomy as a part of the treatment of severe, otherwise intractable hypertension, was originally based upon the idea that attacks upon various parts of the mechanism by which hypertension is maintained might be more effective than treatment more limited in scope. It was our practice at that time to employ the Smithwick thoracolumbar sympathectomy in patients who had proven refractory to combinations of more conservative forms of treatment and who fulfilled the criteria

of eligibility for the operation. In a series of seventeen patients submitted to that operation, unilateral adrenalectomy was also carried out with the idea in mind that later on in patients who had not responded satisfactorily, the combination of subtotal adrenalectomy and thoracolumbar sympathectomy could be achieved by one more operative procedure. Brief preliminary reports of a patient from that series, later submitted to subtotal adrenalectomy with approximately 10 per cent of one gland left in situ have been published.[11] In addition, an account of our earlier experiences with various grades of subtotal adrenalectomy alone and the combination of subtotal adrenalectomy and sympathectomy, mainly a modification of the Adson type abdominal sympathectomy[12] was published in July 1951.[13] Thorn and associates[14] have since reported early effects on hypertension produced by total adrenalectomy, in a series of twelve cases.

Types of Operation and Number in Each Group: The observations to be presented are based upon fifty-four cases in which subtotal adrenalectomy and two in which total adrenalectomy was performed. In twelve, subtotal adrenalectomy and in two total adrenalectomy was the sole surgical procedure employed. In the other forty-two, subtotal adrenalectomy has been combined with sympathectomy. In thirty-three of these, a modified Adson type abdominal operation was performed. In two patients in whom thoracolumbar sympathectomy and one in whom the Peet type thoracic sympathectomy had failed to achieve satisfactory results, subtotal adrenalectomy was performed later. In two, thoracolumbar sympathectomy and subtotal adrenalectomy were done together. In two others, the first stage of combined subtotal adrenalectomy and thoracolumbar sympathectomy was performed, but because of severe postoperative reaction, abdominal sympathectomy in addition to adrenalectomy was performed at the second stage. In two patients originally submitted to subtotal adrenalectomy, sympathectomy was done later in conjunction with an attempt to remove more adrenal tissue. The periods of postoperative observation extend from four to twenty-six months.

In devising procedures, we have had to feel our way along in an almost uncharted field, proceeding on the basis that if marked lowering of blood pressure resulted from operation without unfavorable developments, we were probably on the right track. Obviously much longer periods of postoperative observation are necessary than those

available at this time before definitive judgments can be reached regarding long term rehabilitation. However, observations can be made upon operative mortality and effects of operation upon blood pressure levels, cardiac efficiency, renal and cerebral function, retinal changes and extent of rehabilitation of the patient during the periods of time that have elapsed since operation. The degree of adrenal cortical insufficiency that may be created by subtotal adrenalectomy and its management become problems of primary importance and must be evaluated among the results of operation.

Development of the Operative Procedure: Our first patient, a thirty-three year old, light skinned Negress, had been subjected to thoracolumbar sympathectomy and unilateral adrenalectomy after she had proven refractory to the blood pressure lowering drugs available at that time and had shown little response to severe dietary restrictions, including a rice-fruit diet. Sympathectomy and unilateral adrenalectomy produced temporary modest fall in blood pressure, including a temporary postural fall. When her blood pressure again rose and she again proved refractory to medical treatment, it was decided to complete the subtotal adrenalectomy. Because of the possibility that Green and his colleagues had removed more adrenal tissue than necessary to relieve hypertension, it was elected to leave 10 per cent of the remaining adrenal gland in situ. Only small amounts of replacement therapy were required during the postoperative period and none thereafter aside from a liberal salt intake. Nevertheless she developed a mild pigmentation of the skin. For nearly two years the blood pressure levels have been in the range of 110 to 130 systolic and 70 to 90 diastolic, despite preoperative levels ranging around 230 systolic and 140 diastolic. Following operation she recovered from a state of semi-invalidism and resumed all her household duties, including care of her six year old child. At the time this is written she has successfully completed another pregnancy, being delivered at term by cesarean section of a fully developed apparently normal baby. An eight hour intravenous ACTH test made during late pregnancy more than two years after subtotal adrenalectomy revealed no evidence of adrenal reserve and a metabolic study has demonstrated her need for a liberal intake of sodium chloride. She received 75 mg. cortisone on the day of cesarean section and 25 mg. per day the first three days after operation. There was a slight rise in blood pressure on the day of operation to 160/110 but on the following day

it fell to 133/88. Whether cortisone was responsible for the temporary rise in pressure seems open to question. In any event 25 mg. per day was not enough to maintain elevated pressure.

When it became apparent that hypertension had been abolished and rehabilitation had occurred (at least temporarily) in our first patient, it seemed important to determine whether similar results could be achieved by subtotal adrenalectomy without thoracolumbar sympathectomy, and if so, how much adrenal tissue must be sacrificed to achieve such a result. From the cases in which subtotal adrenalectomy alone was performed, we drew the following tentative conclusions: 1) If adrenal tissue exceeding in amount approximately 10 to 15 per cent of one gland is left in situ, the patient may exhibit no evidence of adrenal insufficiency, but likewise will tend to show little if any significant prolonged fall in blood pressure. 2) If evidences of adrenal insufficiency follow subtotal adrenalectomy, the blood pressure may fall or it may remain elevated. Thus, in two of our patients in whom an attempt had been made to leave in situ 10 per cent of one adrenal gland and 5 per cent of the other, the blood pressure fell to normal, but replacement therapy was necessary. In one other in whom similar amounts of adrenal tissue were left in situ, there was temporary adrenal cortical insufficiency with fall in blood pressure to practically normal levels. Several months later, when replacement therapy was no longer required (regeneration of cortical cells?) the pressure rose moderately but not to the preoperative levels. In two patients in whom approximately 10 per cent of one gland was left in situ, evidences of adrenal insufficiency appeared when replacement therapy was withheld, but the blood pressure remained elevated until nausea, vomiting and extreme weakness developed. The use of amounts of replacement therapy barely enough to relieve such symptoms, caused the restoration of hypertensive levels of pressure. In both of these patients, renal function was regarded as adequate so that failure to obtain a satisfactory blood pressure response could not be attributed to renal insufficiency.

None of the patients in whom subtotal adrenalectomy alone was performed achieved as good a result as the woman in whom this operation had been done following thoracolumbar sympathectomy. This led us to reconsider combined operations. On the basis of experience with subtotal adrenalectomy alone, it seemed likely that the percentage of failures to lower blood pressure would be great if more than 10 per

cent of one gland was left in situ. The fact that the Adson type abdominal sympathectomy[12] is easily combined with adrenalectomy and usually adds no more than fifteen minutes to the operation time on each side, led us to a trial of this operation, slightly modified,* together with subtotal adrenalectomy in the hope that the more extensive but possibly more effective thoracolumbar sympathectomy could be avoided. In the report published in July 1951, it was stated that the early results in 6 cases submitted to this combined operation were promising.[13] Now that the series has been extended to thirty-three cases and postoperative observations are of longer duration, the earlier promise has thus far been fulfilled. However, in a minority of cases, notably in a few with extremely high diastolic blood pressure prior to operation, satisfactory control of blood pressure was not achieved despite the fact that enough adrenal tissue was removed to require replacement therapy in order to avoid symptoms of cortical insufficiency. For this reason *thoracolumbar* sympathectomy instead of *abdominal* sympathectomy has been performed in combination with subtotal adrenalectomy recently in two extremely severe cases. We do not know at present whether the more extensive sympathectomy will increase the effectiveness of the operation, although thus far both of these patients have done well.

Mortality: Thirteen of the fifty-six patients operated on have died. Two who died five and six days respectively after single stage subtotal adrenalectomy, were regarded as operative deaths. Both had advanced hypertensive disease with a group IV Smithwick rating[15] and were recognized to be poor operative risks. Single stage operations were done on the assumption that the risk of one procedure despite the greater duration and trauma involved, might be less than that of two stages. Our subsequent experiences with many equally poor operative risks in which the two-stage procedure was carried out have not supported that view. Postoperative reactions have tended to be less violent with two-stage procedures.

Four patients with poor renal function prior to operation died of progressive renal failure nine to twenty weeks after operation. Another patient succumbed late to acute renal failure which developed following a subsequent operation for strangulated hernia requiring blood trans-

* The ganglia removed were usually T-12, L-1 and 2. The greater and lesser splanchnic nerves were sectioned. No attempt was made to remove the celiac ganglion.

fusion although she lived six weeks despite very little urine output. Two died of recurrent cerebral hemorrhage, one three weeks and the other thirteen months after operation. Three died suddenly, presumably from vascular accidents, but necropsy was not done. One patient died fourteen months after operation. He had been rehabilitated from severe congestive heart failure, had maintained a normal blood pressure and under ordinary circumstances required 3 to 6 mg. of cortisone in order to remain free from symptoms of cortical insufficiency. He was reported by his wife to have developed a respiratory tract infection with slight fever and on the second day, weakness, vomiting and diarrhea, followed by sudden death. Necropsy carried out in a neighboring hospital failed to reveal a cause of death. It seemed probable that death had resulted from adrenal cortical insufficiency precipitated by the combination of infection and gastrointestinal disturbance. The need for a small amount of replacement therapy even when he felt well had been demonstrated by metabolic study a few weeks before death.

The fatalities seemed to warrant the following tentative conclusions: 1) Subtotal adrenalectomy performed in one stage in poor risk patients is probably more hazardous than a two-stage procedure. 2) Patients with severe renal involvement are not improved by (a) subtotal or total adrenalectomy or (b) subtotal adrenalectomy combined with sympathectomy. The blood pressure with rare exceptions has not decreased satisfactorily nor, save in two borderline cases, has the progress of renal disease been arrested. 3) The hazard of sudden vascular accidents is not entirely removed by operation, even though the blood pressure be materially lowered. 4) Unless good cooperation is assured on the part of the patient and in addition someone in close contact with him, the operation should not be done. The cooperation of the patient is required to ensure that he follows orders in all details. The cooperation of someone in close contact with him is needed to report immediately any deviation from the usual state of health because the patient himself cannot be depended upon to carry out orders even in the early stages of adrenal insufficiency.

Blood Pressure Behavior: The success of an operative treatment for arterial hypertension should not be judged entirely by differences in blood pressure readings obtained before and after operation. Smithwick[15] has emphasized the favorable five year mortality record of patients submitted to thoracolumbar sympathectomy. Whether this and

other beneficial effects of that operation, such as relief of headache and regression of eye ground changes in patients who show little change in pressure from the preoperative figures, aside from a temporary postural fall, are attributable to the prevention of surges of extremely high pressure remains an open question. Nevertheless, the relief of hypertension in patients in whom vascular damage or deterioration of cardiac function is developing as a result of high blood pressure would seem to be a highly desirable objective if achieved without the payment of too high a price.

The adrenals, like the thyroid, have a tremendous reserve capacity, which is demonstrated by the fact that only a small fraction of the normal amount of glandular tissue is able to carry on adequate function and maintain the blood pressure at preoperative levels. However, if severe adrenal cortical insufficiency is produced surgically in hypertensive patients, the blood pressure usually, although not always, falls to normal or even to hypotensive levels. Just how the blood pressure lowering effect is achieved is not clear at this time. In the previously hypertensive patient, cortisone alone may be an intensely pressor agent. As little as a 3 mg. difference in daily dosage may sometimes convert a normal blood pressure to a hypertensive level. For this reason dosages of replacement therapy require careful adjustment. Success in preventing return of hypertension may depend on that adjustment.

Because four of the thirteen patients submitted to subtotal adrenalectomy *alone* died within two months after operation, there were only nine cases in which blood pressure behavior is of interest. The postoperative observations, including those made in the two patients who died more than a year after operation, range from eleven to twenty months. In four of the nine, including one who died, the effect of the operation upon blood pressure was negligible. In three, in whom falls in pressure were regarded as satisfactory, the averages of five successive preoperative readings in the hospital with the patient in recumbency, as compared with those of the last five visits have been from 185/135 to 126/86, 234/135 to 141/75 and 205/124 to 138/103. In the remaining two the preoperative and the most recent averages were 200/130 to 166/122 and 190/120 to 164/115, reductions too small to be regarded as satisfactory.

The blood pressure response to the combination of subtotal adrenalectomy and abdominal sympathectomy will be discussed only in the

patients operated on twelve to sixteen months ago. Of the nineteen in this group, four have died—two of progressive renal failure, not arrested by operation, and two died suddenly. One of the latter survived operation eleven months with a fall in blood pressure averages from 242/165 to 132/75. The other who lived five months, had a fall of pressure in recumbency from 222/122 to 177/109, but the averages of postoperative pressures when she was erect were 125/108. Among the fifteen survivors eight have been regarded as having a satisfactory fall in pressure. The preoperative and most recent averages of pressure in recumbency for these eight patients are as follows: 204/118 to 132/91, 234/133 to 142/88, 224/133 to 147/108, 231/122 to 155/100, 193/119 to 154/107, 212/116 to 151/98, 212/145 to 143/105 and 200/126 to 141/99. In three, the average falls in pressure were moderate, 191/128 to 145/112, 229/149 to 161/111 and 243/132 to 186/110. In four, the falls in pressure were slight to insignificant: 253/125 to 219/133, 218/152 to 201/144, 181/119 to 176/111 and 204/122 to 178/116. In the fourteen additional patients operated on less than nine months ago, the results thus far are at least as good as in the older group. The single death thus far in this more recent series is the one mentioned above which followed operation for intestinal obstruction.

No definite comparison of effects on blood pressure can be made between the group in which *subtotal adrenalectomy alone* was performed and that in which the same operation was combined with *abdominal sympathectomy*. In the former, some of the unsatisfactory results may be accounted for by the fact that too much adrenal tissue was left in situ. Moreover all of the patients in that series were poor risks, eleven of the thirteen falling in Smithwick's Group IV, whereas only eight of the nineteen patients in whom results of the combined operation are considered here fell in Group IV. One striking difference is that a postural fall in pressure occurs in most cases after the combined operation, whereas it is the exception rather than the rule after subtotal adrenalectomy alone. Nevertheless, adrenal replacement therapy, given in amounts that raise the blood pressure level when the patient is supine, tends to prevent a fall to extremely low levels when he stands. Nine of the fifteen patients surviving twelve to sixteen months after the combined operation still exhibit a definite postural fall in pressure. Some of these receive larger doses of replacement therapy than are required by their metabolic needs. This is done to try to prevent pos-

tural fall of pressure to levels that might cause objectionable symptoms. Six of the fifteen patients in this series in whom less than 10 per cent of one adrenal gland was left in situ, require no replacement therapy. Included among these are two in whom the blood pressure has remained at high levels.

Cardiac Effects: In the entire series, there were nine patients subject to congestive heart failure prior to operation. Five of these could not be relieved completely even during hospital care. In two, subtotal adrenalectomy was performed and in seven, the combined operation. All survived operation and were completely relieved of congestive failure, although one referred to above died fourteen months after operation, presumably because of neglect in following instructions when he developed an infection. A few of these patients still receive small doses of digitalis, although the need for it is no longer demonstrable. All are relieved of symptoms. The hearts which had been markedly enlarged are now either normal in size or only slightly enlarged. In one patient without congestive failure but subject to anginal pain on exertion, a satisfactory fall in blood pressure was achieved by the combined operation. Although his exertion tolerance has improved, he has not been completely relieved of his tendency to develop anginal pain.

Some unfavorable cardiac results have been observed. One patient developed acute infarction of the posterior wall of the left ventricle during convalescence from the second stage of a combined operation. At the time, his blood pressure showed a fall to unobtainably low levels on standing. He has made an excellent recovery and has been able to return to full time employment. Two other patients had mild episodes of chest pain with associated minor electrocardiographic changes. Both have made an excellent recovery. One of the patients in whom subtotal adrenalectomy alone failed to control hypertension developed an attack of severe pain in the chest (without significant change in electrocardiograms) during convalescence from operation, followed by low grade fever for a week and severe congestive heart failure requiring prolonged treatment with digitalis and mercurials. He eventually recovered from heart failure but then developed a mild anginal syndrome. The heart which had been greatly enlarged prior to operation was not diminished in size nearly a year after operation. During the period of congestive failure, reduction of replacement therapy to a point where he developed

symptoms of Addison's disease did not relieve him of fluid retention. The requirement for replacement therapy gradually lessened, finally disappeared and he became able to tolerate salt restriction without reduction of blood pressure. Recently he exhibited a normal eosinophile response and normal increase in output of 17-ketosteroids following an eight hour ACTH test. For these reasons reoperation was undertaken approximately a year after the original operation. The adrenal fragment was healthy in appearance but apparently had not increased in size. About half was removed. A Smithwick thoracolumbar sympathectomy was performed on the same side and twelve days later thoracolumbar sympathectomy was carried out on the other side. Marked fall in pressure, although not to normal levels, developed after the first of these operations, replacement therapy was again required and for the first time postural hypotension was observed. Further fall in pressure developed after the second operation. Before leaving the hospital the heart for the first time exhibited significant reduction from its previously enormous size.

Renal Function: The greatest single cause of poor results in this study has been kidney disease advanced enough to cause serious impairment of renal function. Thus, such findings as inability to excrete 15 per cent of phenolsulphonephthalein in fifteen minutes, a blood urea nitrogen level persistently above 20 mg. per cent (in the absence of congestive heart failure), urea clearance below 40 per cent of average normal function, we now believe should contraindicate adrenalectomy. Our disappointing results in patients with advanced renal disease appear to be much the same as those observed by Thorn and his colleagues in similar cases following total adrenalectomy.[14]

Thus far we have noted little improvement of renal function even in patients with reduction of blood pressure to normal levels for many months, although Clark, Crosley and Barker[16] have shown in some of our patients that slight increase in effective renal plasma flow may occur.

Cerebral Circulation: Studies of cerebral blood flow and cerebral oxygen consumption made before and after operation in seven cases showed little change in values.[17] Similar results had been obtained before and after thoracolumbar sympathectomy. Thus it appears that following either one of these operations cerebral blood flow tends to be maintained at a fairly constant rate throughout a wide range of blood pressure levels by a mechanism which adjusts cerebral vascular resistance.

The Eye Grounds: Marked improvements have been observed in the ocular fundi after operation.* Swelling of optic discs if present usually vanishes promptly as pressure falls. Likewise retinal hemorrhages diminish or cease and exudates disappear. Attenuation of arterioles lessens and A-V crossing indentations slowly become less marked. To what extent changes in the eye grounds may reflect similar changes in the cerebral circulation is not known. Many hypertensives with advanced changes in the fundi exhibit no evidences of deterioration of cerebral function. However, in two of our patients with Grade IV hypertensive retinopathy (Keith-Wagener) and dulling of mental acuity, improvement in appearance of the fundi and significant increase in mental acuity began before they left the hospital.

Discussion

The Hemodynamics of Hypertension with Reference to Treatment: Arterial blood pressure obviously results from the interaction of the other circulatory forces and the motions which are included under the convenient term "hemodynamics." Thus, irrespective of neurogenic or humoral activities which influence circulatory functions and which must therefore exert effects upon blood pressure, a satisfactory understanding of the mechanism by which blood pressure regulation is achieved scarcely seems possible until some of the gaps in our knowledge of hemodynamics are filled.

Wiggers has stated in the 1949 Edition of his textbook[18] that under normal conditions only three factors can be concerned in producing alterations in mean distention of the arterial system and therefore the mean arterial pressure, namely an alteration in heart rate, a change in systolic discharge and variations in the run-off from the arterial system caused by active changes in the size of the arterioles and perhaps of the capillaries. Wiggers' views on the hemodynamic aspects of blood pressure regulation appear to be in accord with those of most physiologists and usually are accepted as the basis for discussions of the hemodynamics of hypertension. Probably because of the fact that measurements of cardiac output do not tend to fall outside the normal range in hypertensive states unless or until cardiac complications develop, the emphasis has been on arteriolar vasoconstriction as the initiating hemodynamic disturbance responsible for hypertension.

* These observations were made by Drs. Francis H. Adler, Harold G. Scheie, Irving H. Leopold and George Tyner.

It now appears that in certain important vascular beds, changes in peripheral resistance serve the purpose of maintaining relatively constant flow rather than regulation of pressure. This has been most convincingly demonstrated in the case of the cerebral circulation by studies such as those cited above.[17] The studies of Clark, Crosley and Barker on renal hemodynamics[16] before and after operation in some of our previously hypertensive patients support the view that resistance serves a similar purpose in the kidneys. Recent observations by Crumpton and Murphy[19] indicate that when drastic reduction of the mean arterial pressure is produced by hexamethonium bromide in previously hypertensive dogs, coronary flow shows little change (actually a slight increase). To what extent peripheral resistance in various other parts of the systemic circulation may be concerned primarily in the regulation of flow rather than pressure does not appear to be clearly established at this time, save under special circumstances such as blood supply to skeletal muscles when work is being performed.

The evidence that in various important vascular beds peripheral resistance serves the purpose of regulating flow rather than pressure raises questions of basic importance both to physiologists and to clinicians. Relevant to hypertension, the validity of at least two widely accepted and frequently emphasized current views appear to merit reconsideration. 1) Do we need to fear drastic lowering of blood pressure because the new low head of pressure will be unable to force blood through vasoconstricted arteriolar channels? We had already learned from the blood pressure behavior of hypertensives following acute coronary occlusion that despite probable great reduction in cardiac output, cerebral and renal function are often well maintained until the blood pressure falls to extremely low levels. In the present study, reduction in blood supply to the heart, brain and kidneys as judged by the preservation of function of those organs following marked fall in blood pressure, has not been a major problem. However, the oft discussed possibility that a marked reduction of pressure may upon occasion favor occlusion of an artery at the site of pre-existing disease had to be considered and could not be excluded in a few of our patients. 2) If we think that the hemodynamic alterations in hypertension must be initiated and maintained by vasoconstriction of arterioles or perhaps metarterioles and precapillary sphincters, may we not be in danger of accepting an unnecessarily narrow view of the

problem that may close our minds to certain possibilities of treatment?

Lack of methods for measuring the volumes of arterial and venous reservoirs, the tonus of vessels and their distensibility under various conditions, may have constituted a greater handicap to an understanding of the hemodynamics of blood pressure regulation than has been generally realized. Peterson[20] has recently devised an experimental procedure whereby a volume pulse is introduced within the vascular tree such that the rate of change of volume has the form of a square wave. In this way, the pressure resulting from both volume change and acceleration of flow may be studied. By the use of this procedure he has recorded characteristics of the pressure pulses produced in both venous and arterial systems. Although his work is still admittedly in a preliminary stage, Peterson has presented evidence to indicate the importance of certain factors heretofore usually not taken into account. His results indicate that the rate of change of velocity of blood flow as the aortic valve opens may make a major contribution to the pulse pressure. This early steep rise in pressure which he calls the "acceleration transient" may be relatively large when the volume ejected is relatively small. It would appear also that arterial distensibility, arterial volume including volume change with time, and vascular tone influence the pressure pulse. Peterson's results tend to support views of the late H. C. Bazett[21] that arterial distensibility and volume of the arterial reservoir may exert important effects on blood pressure. The marked effect of rate of change of velocity of flow upon pulse pressure appears not to have been anticipated.

It seems to be generally agreed that total peripheral resistance in the arterial tree can be calculated with a fair approach to accuracy on the basis of measurements of cardiac output and mean arterial pressure. Thus when mean arterial pressure changes, it may be assumed that cardiac output or peripheral resistance or both also change. If, however, the chief function of peripheral resistance is to maintain constancy of flow in large important vascular beds, the total run-off from the other vascular beds must remain normal provided cardiac output does not change. Consequently we must consider the possibility that mechanisms not necessarily limited to effects upon arterioles may initiate and help to maintain disturbances of pressure. In the present state of our knowledge the matter is a subject for investigation rather than extended discussion. The point we wish to make here is that the arteries

and veins may also play an important but at present undetermined part in blood pressure regulation. For example, increased tone or constriction of the venous system could be expected to lead to transfer of blood from the venous to the arterial reservoir. If such a transfer took place and if run-off from the capillaries were maintained at a normal level by appropriate adjustment of peripheral resistance, the arterial reservoir must expand and with it the arterial walls. Changes in the degree of arterial wall tone and in the response of the wall to the stress of a systolic discharge also must occur producing an effect upon arterial blood pressure requiring a further readjustment of peripheral resistance to maintain flow at a constant level. It is also conceivable that elevation of pressure might be initiated by increase in tone of the arterial tree without a temporary increase in cardiac output but with increase of total peripheral resistance to prevent increase in blood flow.

High arterial blood pressure can be lowered only by procedures which interfere with the interaction of hemodynamic factors by which hypertension is maintained. Theoretically this might be accomplished by a direct attack on one or more parts of the hemodynamic mechanism or by an attack on neurogenic or hormonal influences that help to maintain the hemodynamic support for hypertension. In accordance with the widened concept of the hemodynamic control of blood pressure suggested above, one is not necessarily limited in treating hypertension to the election of measures designed solely to combat either an assumed neurogenic or hormonal altered function of arterioles. We have proceeded upon the assumption that hypertension, irrespective of its etiology or pathogenesis, may be open to attack upon a wide hemodynamic front by means of either the neurogenic or hormonal control or both. The pressure response may not depend wholly upon a single hemodynamic change as it presumably does after myocardial infarction. Fall in pressure might result from the additive effects of interference with neurogenic and hormonal control of a single hemodynamic function or upon a combination, no one of which alone would be capable of producing a decisive effect. In this connection it may be of interest to comment upon certain aspects of the behavior of orthostatic hypotension. A postural fall in pressure (often temporary) tends to develop after splanchnic denervation. As stated above, subtotal adrenalectomy alone does not tend to produce a postural fall in pressure. Nevertheless subtotal adrenalectomy can produce postural hypotension in patients

previously subjected to sympathectomy as was clearly demonstrated in two of our cases. This would appear to be an example of additive effect produced by the combination of disturbance of neurogenic and humoral blood pressure regulating mechanisms. The possibility that additive effects might operate upon blood pressure levels independently of such special conditions as those created by change in posture was what moved us to combine subtotal adrenalectomy with sympathectomy. The observation that patients whose blood pressure was not satisfactorily lowered by operation are sometimes more responsive than before operation to blood pressure lowering drugs,[22] might be accounted for by additive effects. Conceivably such effects might be exerted upon the same part or upon different parts of the hemodynamic mechanism. Completely satisfactory studies of such problems are not possible at this time because some of the requisite measurements cannot be made.

Adrenal Function and Blood Pressure Control: If adrenalectomy is to achieve a place for itself in the treatment of essential hypertension, it becomes important to ascertain whether the best results will be achieved by attempting to leave in situ as much adrenal tissue as is consistent with the objective of lowering blood pressure, or whether nearly total adrenalectomy[10] or total adrenalectomy[14] should be done. Advantages of total adrenalectomy are 1) avoidance of failure to lower pressure because at operation too much adrenal tissue is left in situ (unless a functioning cortical rest exists), 2) regeneration of an adrenal fragment cannot occur, and 3) interpretations of metabolic studies and effects of replacement therapy are not obscured by an uncertain amount of adrenal cortical function. Despite these manifest advantages of total adrenalectomy, it seemed to us important to explore the possibility that the amount of adrenal cortical function necessary to sustain hypertensive levels of blood pressure might be less than that required to maintain the patient in a state of health. This problem is still not settled. In none of the few patients in whom adequate postoperative studies have been made thus far (irrespective of whether or not replacement therapy is required) can we assert that we have been able to reduce blood pressure from hypertensive levels to normal or even nearly normal by adrenalectomy without producing changes that could be regarded as evidence of at least slight adrenal cortical insufficiency. The important practical problem is whether such patients can be maintained indefinitely in a state of well-being with blood pressure levels in the neighborhood of

normal or at least greatly reduced from the preoperative range. That the majority of properly selected patients can be so maintained following the combined operation has been demonstrated so far as the periods of observation extend.

Effect of Subtotal Adrenalectomy Upon Cardiac Failure: The relief of congestive heart failure in hypertensive patients following subtotal adrenalectomy irrespective of whether sympathectomy is also done is comparable to the relief of similar grades of congestive failure in hyperthyroid patients following effective treatment of the hyperthyroidism. Because of the fact that the combination of hypertension, congestive failure and increase in heart size, can be produced by overdosage of DCA (desoxycorticosterone acetate),[23-25] it might be postulated that the improvement in the cardiac status of these patients is caused by reduction in the DCA-like hormone effect. The possibility that the improvement is due solely to relief from the burden imposed upon the heart by high blood pressure has not been excluded. However, the prompt improvement that may occur without much lowering of pressure, in contrast to our experience with the course of congestive failure following thoracolumbar sympathectomy, suggests that sodium excretion after adrenalectomy may be an important factor in the relief of congestive failure. Irrespective of the mechanism, chronic or recurring congestive failure in a hypertensive furnishes a strong indication for subtotal adrenalectomy, provided renal function is not seriously impaired. So far as we are aware, it is far superior to any other form of treatment now available.

Sympathectomy versus the Combined Operation: Among the many points of disagreement among workers on hypertension is the status of sympathectomy, despite the many years such operations have been performed, the vast amounts of data accumulated, and the careful studies that have been made. At least four different types of operation varying in extent from total removal of the ganglionic chains to limited abdominal sympathectomy are currently recommended, each type of operation having strong supporters. With regard to the indications for operation, it may be said that, in general, the younger the patient, the shorter the duration of hypertension and the less severe the hypertensive process in terms of vascular deterioration or cardiac exhaustion, the better the state of the patient after operation. Many workers are not greatly impressed by such facts and point out that patients with relatively mild

hypertensive disease may live a long time and do very well without operation. Moreover, they point to the fact that in many patients the blood pressure is not lowered materially after operation aside from the temporary postural fall in pressure. The most effective rebuttal against the conservative position is that of Smithwick[15] who points to his statistics showing a significantly lower mortality over five year periods. The lower mortality applies to the relatively mild cases included in his Groups I, II and III. The five year mortality of patients with severe hypertensive disease is little improved by operation although headache may be relieved and the progress of retinopathy may be arrested.

Our experience with thoracolumbar sympathectomy, although limited in comparison with that of Smithwick, appears to be in agreement with his observations. We have been somewhat discouraged by the tendency of blood pressure with the passage of time to creep back toward the preoperative level. This tendency, observed by others, has led to such suggestions as regrowth of the sectioned portions of the sympathetic nervous system, or increase in effectiveness of sympathetic activity via neurons which presumably do not enter the ganglia and thus escape division. However, it seems possible that certain physiologic readjustments gradually substitute at least in part for the effect of the lost sympathetic function upon blood pressure. This conceivably might be the intrinsic mechanism within the walls of the blood vessels or it might be a humoral mechanism stimulated to increased activity because of the loss of sympathetic nerve function. It is this readjustment to sympathectomy which apparently more than anything else impairs its effectiveness and renders prediction tests based on effects of so-called sympatholytic drugs unreliable. In fact, loss of effectiveness of certain drugs in the treatment of hypertension may be due to the same type of readjustment that occurs after sympathectomy.

If one could neutralize the readjustment or compensation for loss of sympathetic nerve function after sympathectomy, this alone would probably constitute a great advance in treatment. If the compensatory mechanism that develops following sympathectomy happens to be humoral, the possibility that adrenalectomy, aside from its own effects in lowering blood pressure, might block this mechanism and render sympathectomy far more effective deserves exploration. Our data do not permit nor even suggest an answer to such a question. The fall in

blood pressure after adrenalectomy alone, aside from a very early fall frequently noted within twelve to twenty-four hours after operation, which is not sustained, is slow and gradual over the course of a month or two. The pressure may then remain low or there may be a slow but usually limited increase. In contrast is the precipitous fall in pressure after sympathectomy, which is at its maximum as soon as severance of the nerves is completed (unless shock occurs later). These two different forms of behavior appear to indicate two different forms of attack upon the mechanism of hypertension. When the two procedures are combined, the pressure not only tends to drop promptly, but stays down in the successful cases unless excessive dosage of replacement therapy is administered. This behavior is the greatest point of superiority of the combined operation (and in some cases adrenalectomy alone) over sympathectomy.

We are not ready at this time to recommend the adoption of procedures such as those described here, except to groups interested in the investigative problems of hypertensive disease. This is still an investigative project which we hope will provide information leading to the development of far less radical but at least equally effective methods of treatment. There is at present, no justification for applying these procedures to patients who respond to conservative forms of treatment or to those with a reasonably good prognosis. They should be applied only to patients who have little to lose, those in whom vascular deterioration is progressive to the point that they are threatened with impairment of vision, deterioration of cerebral function, intractable cardiac failure or uremia. However, if patients are to derive benefit they must be operated on before renal failure is in too advanced a stage or before hopeless stages of cerebral damage have occurred.

Summary

1. A study has been made of the applicability of adrenalectomy to the treatment of severe, otherwise intractable arterial hypertension. The present report deals with fifty-six cases with periods of postoperative observation ranging in duration from twenty-six to four months.

2. The amount of adrenal tissue capable of maintaining patients in a state of satisfactory health, in the absence of special stress such as severe infection, is relatively small. In some, no more than 5 per cent of

the total adrenal mass appears to be adequate for that purpose.

3. It has not been demonstrated thus far that reduction of arterial blood pressure from hypertensive levels can be achieved by adrenalectomy unless at least slight adrenal cortical deficiency is produced. Thus, failure to control hypertension will occur frequently if less than 95 per cent of the adrenal tissue is removed. The relative merits of subtotal versus total adrenalectomy in the treatment of severe hypertension have not yet been established.

4. It has been our impression to date that better control of blood pressure levels and more satisfactory clinical results are obtained by combining either abdominal sympathectomy and splanchnicectomy or thoracolumbar sympathectomy with subtotal adrenalectomy than are achieved by the latter operation alone. Further studies bearing on these problems will be required.

5. Thirteen of the fifty-six patients subjected to adrenalectomy have died. The survival rate could be improved materially by 1) rejection of patients with advanced renal disease, and 2) avoidance of single-stage operations. An occasional death from a vascular accident at some time after operation appears to be unavoidable in patients with advanced vascular disease even though marked reduction of blood pressure is achieved.

6. The indications for adrenal cortical replacement therapy after adrenalectomy have been discussed. The possible sudden increase in requirements as a result of infection, gastrointestinal disturbance, extremely hot weather, or other forms of stress, must be kept in mind even in those who ordinarily require no replacement therapy. Failure to observe such precautions may lead to the rapid development of severe adrenal insufficiency or even to death if readjustment of treatment is delayed too long.

7. Subtotal adrenalectomy with or without sympathectomy has exhibited a remarkable beneficial effect upon nine cases of congestive heart failure complicating hypertensive disease. It is suggested that this improvement may be attributed in part to lowering of blood pressure and in part to altered regulation of electrolytes. Because of the results obtained in these patients, it now appears that intractable or frequently recurring congestive heart failure in a hypertensive, unless too severe to warrant the hazard of operation, constitutes a positive indication for subtotal adrenalectomy.

8. The results of subtotal adrenalectomy with or without sympathectomy have been disappointing in hypertensives with advanced impairment of renal function. The degree of reduction in blood pressure has tended to be progressive. In patients with lesser grades of renal involvement, lowering of pressure and general improvement may occur although little improvement in renal function has thus far been observed.

9. Marked improvement in so-called hypertensive retinopathy has been observed in the vast majority of patients. At least two and possibly five cerebral vascular accidents resulting in death have occurred at some time following operation. Two patients with advanced mental deterioration and retinopathy exhibited great improvement in mental acuity which seemed to parallel roughly improvement in the ocular fundi.

10. The results obtained in this study have been encouraging enough to warrant continuance of investigation. The project is not yet far enough advanced to justify recommendations for the widespread clinical adoption of the operative procedures thus far employed. There is at present no justification for submitting hypertensives with a reasonably good prognosis to such formidable procedures.

11. A brief analysis of the current status of knowledge of the hemodynamics of blood pressure regulation is presented. It is concluded that reasons which have thus far been advanced to limit attempts at treatment of arterial hypertension to the neurogenic or possibly the hormonal aspects of arteriolar function are not firmly established. The treatment of arterial hypertension, save in the limited group of cases in which the cause can be eradicated, must remain, at least for the present, upon an empirical basis.

Since this paper has gone to press, Thorn and his associates have again reported on the results of bilateral complete adrenalectomy in patients with severe hypertensive vascular disease. As in our experience, the results in patients with advanced renal insufficiency were unfavorable. Relief from heart failure was pronounced. (Clinical Studies on Bilateral Complete Adrenalectomy in Patients with Severe Hypertensive Vascular Disease, by George W. Thorn, J. Hartwell Harrison, John P. Merrill, Modestino G. Criscitiello, Thomas F. Frawley and John T. Finkenstaedt. Ann. Int. Med. Vol. 37, No. 5, p. 972, November 1952.)

ACKNOWLEDGMENTS

William T. Fitts performed the operation of subtotal adrenalectomy in two of the cases included in this report and directed the surgical aspects of postoperative care in those cases.

F. Curtis Dohan and E. M. Richardson have carried out the studies of corticoid and 17-ketosteroid excretion.

Francis D. W. Lukens has been an active collaborator in the earlier phases of this work. He continues to serve as a consultant.

David P. McCallie and Richard S. Wilbur have had charge of many of the patients and have collected data.

The Misses Nelly Jane Keffer, Janet Merrill and Henrietta Brandt have made daily blood pressure readings when patients were in the hospital and on return visits, including postural tests whenever possible. They have helped prepare various tables.

Generous supplies of adrenal cortical extract have been furnished by the Upjohn Company.

Merck and Company, Inc. has supplied the large amounts of aqueous suspension and tablets of Cortone used in this study.

Ciba Company has furnished DCA for both oral and parenteral use.

The Schering Company has supplied DCA for both oral and parenteral use.

REFERENCES

1. Loeb, R. F. The adrenal cortex and electrolyte behavior, *Bull. N. Y. Acad. Med. 18*:263-88, 1942.
2. Case Records of the Massachusetts General Hospital. Case 34502, *New Engl. J. Med. 239*:933-37, 1948.
3. Goldblatt, H. Renal origin of hypertension, *Physiol. Rev. 27*:120-65, 1947.
4. Crile, G. W. *Surgical treatment of hypertension.* Philadelphia, W. B. Saunders Co., 1938.
5. DeCourcy, J. L. Subtotal bilateral adrenalectomy for hyperadrenalism (essential hypertension), *Ann. Surg. 100*: 310-18, 1934.
6. DeCourcy, J. L. Hypertension treated by subtotal bilateral adrenalectomy, *J. int. Coll. Surg. 13*:619-22, 1950.
7. Leriche, R. Du choix d'une methode dans le traitement chirurgical de l'hypertension arterielle, *Arch. méd. belges 95*:575-79, 1942.
8. Neuhof, H. Gangliosympathectomy and bilateral hemiadrenalectomy for severest grade of hypertension, *Ann. Surg. 128*:787-90, 1948.
9. Green, D. M., Nelson, J. N. and Dodds, G. A. Effects of adrenal resection on hypertension and diabetes (abstract), *Fed. Proc. 8*:60-61, 1949.
10. Green, D. M., Nelson, J. N., Dodds, G. A. and Smalley, R. E. Bilateral adrenalectomy in malignant hypertension and diabetes, *J. Amer. med. Assoc. 144*:439-43, 1950.
11. Hafkenschiel, J. H., Jeffers, W. A., Lukens, F. D. W., Zintel, H. A., Keffer, N. J. and Wolferth, C. C. Subtotal

adrenalectomy in essential hypertension: postural blood pressure responses in relation to type of cortical replacement therapy (abstract), *Amer. J. Physiol. 163:*719, 1950.

Lukens, F. D. W., Wolferth, C. C., Jeffers, W. A., Zintel, H. A. and Hafkenschiel, J. H. Observations on subtotal adrenalectomy in hypertension, *Trans. Amer. clin. climat. Assoc. 62:*229-36, 1950.

Zintel, H. A., Wolferth, C. C., Jeffers, W. A., Hafkenschiel, J. H. and Lukens, F. D. W. Ninety-five per cent subtotal adrenalectomy for essential hypertension, *Surg. Forum (Proc. clin. Congr. Amer. Coll. Surgeons)* 1950:556-58.

12. Adson, A. W., Craig, W. McK. and Brown, G. E. Surgery in its relation to hypertension, *Surg. Gynec. Obstet. 62:*314-31, 1936.
13. Wolferth, C. C., Jeffers, W. A., Lukens, F. D. W., Zintel, H. A. and Hafkenschiel, J. H. Observations on the results of subtotal adrenalectomy in the treatment of severe, otherwise intractable hypertension and their bearing on the mechanism by which hypertension is maintained, *Ann. intern. Med. 35:* 8-18, 1951.
14. Thorn, G. W., Harrison, J. H., Criscitiello, M. G. and Frawley, T. F. Physiological changes following bilateral total adrenalectomy in patients with advanced hypertensive vascular disease. *Trans. Assoc. Amer. Phycns. 64:*126-33, 1951.
15. Smithwick, R. H. The effect of sympathectomy upon the mortality and survival rates of patients with hypertensive cardiovascular disease, in *Hypertension* (E. T. Bell, ed.), Minneapolis, University of Minnesota Press, 1951, p. 429.
16. Clark, J. K., Crosley, A. P., Jr. and Barker, H. G. Effect of subtotal adrenalectomy on renal hemodynamics and electrolyte excretion in human hypertension (abstract), *J. clin. Invest. 30:*633, 1951.
17. Hafkenschiel, J. H., Friedland, C. K. and Crumpton, C. W. Subtotal adrenalectomy in essential hypertension: preliminary report of the effects on cerebral hemodynamics and oxygen metabolism (abstract), *Amer. J. Physiol. 167:* 790, 1951.
18. Wiggers, C. J. *Physiology in health and disease.* 5.ed. Philadelphia, Lea and Febiger, 1949, p. 606.
19. Crumpton, C. W. and Murphy, Q. R. Effects of hexamethonium bromide upon hemodynamics of cerebral and coronary circulation in hypertension (abstract), *J. clin. Invest. 31:*622, 1952.
20. Peterson, L. H. Certain aspects of reflex and mechanical influences upon venous circulation (abstract), *Fed. Proc. 11:*122, 1952.
21. Bazett, H. C. Physical factors in the circulation, in *MacLeod's physiology in modern medicine.* 9.ed. St. Louis, C. V. Mosby Co., 1941, chapter 32, pp. 405-438.
22. Hafkenschiel, J. H., Jeffers, W. A., Lindauer, M. A., Zintel, H. A., Kuo, P. T., Friedland, C. K., McCallie, D. P., Hills, A. G. and Wolferth, C. C. Experiences with new depressor drugs before and after subtotal adrenalectomy alone or combined with sympathectomy, *Scientific Session American Heart Assoc.*, Cleveland, Ohio, April 19, 1952.
23. Loeb, R. F., Atchley, D. W., Ferrebee, J. W. and Ragan, C. Observations on effects of desoxycorticosterone esters and progesterone in patients with Addison's disease. *Trans. Assoc. Amer. Phycns. 54:*285-96, 1939.
24. Perera, G. A., Knowlton, A. I., Lowell, A. and Loeb, R. F. Effect of desoxycorticosterone acetate on blood pressure of man, *J. Amer. med. Assoc. 125:*1030-35, 1944.
25. Thorn, G. W., Forsham, P. H. and Emerson, K., Jr. *The diagnosis and treatment of adrenal insufficiency.* Springfield, Ill., C. C. Thomas, 1949, chapter 14.

RECENT ADVANCES IN DERMATOLOGY*

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THE subject for discussion today is "Recent Advances in Dermatology." Some of the advances I propose to discuss represent strictly dermatologic accomplishments, others are primarily applications of general medical and laboratory advances to dermatologic problems. Since time will not permit a discussion of all subjects which currently might deserve review, I shall select for consideration a few topics which on the basis of my own appraisal seem to me to be the most significant.

THE USE OF ACTH AND CORTISONE IN DERMATOLOGY

I suppose that many of us would agree that the most striking development in medicine during the past two years has been the use of ACTH and cortisone in the treatment of various diseases. This certainly has been true in dermatology where studies on the use of corticosteroids in the treatment of various dermatoses seem to have overshadowed other items of progress in the field. Already a long list of dermatologic conditions which have been treated with ACTH and cortisone has been compiled. For the most part, the early reports were very enthusiastic and emphasized the remarkable rapidity with which these hormones achieved results in a number of different skin disorders. Later on, as some of their undesirable physiological effects were noted and their therapeutic shortcomings became known, the estimates of their usefulness became more conservative.

As in other fields, we have now found that these compounds are not curative. Sometimes they do bring about remissions but, in general, unless the disease is by its nature a self-limited one, the compounds are of benefit only as long as adequate dosage is continued. This necessity for maintenance therapy and the frequency of undesirable side effects indicate that ACTH and cortisone are no dermatologic panaceas. It

* Presented in the Friday Afternoon Lecture Series at The New York Academy of Medicine, April 4, 1952. Manuscript received for publication May 15, 1952.

can be hoped, however, that in dermatology, as in other branches of medicine, these hormones will become valuable new tools for basic investigations of the mechanisms of certain diseases and metabolic processes.

The ability of ACTH and cortisone to suppress certain types of allergic reactions as well as some inflammatory processes which are not primarily allergic in origin, probably explains in large measure their beneficial effect in cutaneous diseases. Apparently ACTH and cortisone will sometimes permit tissue cells to live in a hostile environment without showing the usual signs of damage. Although we cannot yet offer any final conclusions, it is possible to evaluate in a general way the results of the treatment of cutaneous diseases with these hormones. In summarizing our present knowledge of the response of various dermatologic conditions to ACTH and cortisone, I should like to point out that several of the diseases listed as being benefited by these compounds (e.g., drug eruptions, erythema multiforme, erythema nodosum, acute urticaria, anaphylactoid purpura, and contact dermatitis) are allergic manifestations. These are of limited duration—if the precipitating cause can be found and eliminated. In these, the use of the hormones is often beneficial since the remission induced may easily be prolonged enough to cover the natural evolution of the disease. In other conditions such as intrinsic allergic eczema (atopic dermatitis), psoriasis, chronic discoid lupus and dermatitis herpetiformis, the results are not nearly as gratifying. These are chronic, but usually not serious dermatoses, in which treatment with ACTH or cortisone is followed by some improvement. However, the patients almost invariably relapse forcefully after the corticosteroids are discontinued. Many of these patients are unable to reconcile themselves to a return of their dermatitis and they become insistent in their demand for more treatment, with all of its possible complications. In this group of dermatoses, therefore, ACTH or cortisone would be indicated only in exceptional cases.

Other diseases that we may mention include some serious and frequently fatal skin disorders in which corticosteroids represent the best treatment available at this time and in which their use is definitely indicated. Systemic lupus erythematosus and pemphigus certainly belong to this group. Once started, the treatment very probably must be continued for long periods of time—but this is a minor consideration when the patient's life is at stake. Whether or not the ultimate fatality rates in

these conditions (e.g., five years from now) will be significantly modified by ACTH or cortisone is not known. The situation now seems a little more hopeful, however, since up to now we usually have not been able to keep the patients with these diseases alive long enough to learn if a permanent spontaneous remission can be attained.

In summary, we may say that treatment with ACTH or cortisone has given worthwhile results in cases of systemic lupus erythematosus, pemphigus, some forms of sarcoidosis, certain types of generalized exfoliative dermatitis, drug eruptions and other allergic dermatoses of the self-limiting type. For these the hormones may be recommended on the basis of relief of symptoms but not from the point of view of cure. ACTH and cortisone are not considered to be effective in uncomplicated psoriasis, the usual eczematous patient, chronic discoid lupus or lymphoblastoma of the skin.

In addition, although other investigators have had encouraging results in the treatment of scleroderma and dermatomyositis with these compounds, our results in a fairly large series of cases have been quite disappointing. In dermatomyositis we have not observed much improvement in cutaneous edema, induration, muscle strength, and muscle function—and biopsies of muscle after corticosteroid therapy have shown little histological improvement. Insofar as scleroderma is concerned, ACTH and cortisone seem to afford some subjective relief in early cases—at least the patients feel more comfortable, are in better spirits and have improved appetites. They have less joint pain, less dysphagia, and feel that the skin is more supple. In the more advanced cases of this disease such subjective improvement has been less noticeable and in none of our cases have the objective signs of the disease improved on hormone therapy. Skin temperature, pulmonary gas exchange and esophageal changes as seen by x-ray have not improved and in biopsies of the skin we have not seen the thinning out and loosening of the collagen bundles observed by some investigators.

Before leaving the subject of the corticosteroids something should be said about the complications of ACTH and cortisone therapy. The physiological effects of these hormones are now well known and the occurrence of a Cushing-like syndrome, alterations in electrolyte metabolism, hyperglycemia, elevated blood pressure, calcium loss and osteoporosis should be familiar to all physicians.

Of all the complications of corticosteroid therapy, perhaps the most

important and most disturbing one is the inability of the patient receiving the hormones to handle infectious processes. Furunculosis and other pyogenic skin infections, abscess formation at the sites of injection, pneumonias and spread of pre-existing tuberculosis are some of the more important ones. Thromboembolic complications have also been relatively common in our cases and we feel that thrombotic phenomena should be considered to be one of the serious complications of this type of therapy. Mental disturbances have also not been unusual in our patients and, of course, have usually necessitated discontinuance of the hormones. The frequency of the development of peptic ulcers in patients receiving ACTH or cortisone has also been impressive in our series of cases. In two instances perforations have occurred before the attending physicians realized that a peptic ulcer was present. Only recently I saw the fourteenth patient at the Columbia-Presbyterian Medical Center who had developed a peptic ulcer without having had symptoms or signs of such a condition prior to the administration of the corticosteroids.

Dosage schedules for treatment with ACTH and cortisone require no comment since they are already well known to practicing physicians. Regarding any differences in the results of treatment with ACTH on the one hand and cortisone on the other I think it is fair to say that we have observed no differential therapeutic effect between the two compounds. If the patient has an adrenal cortex and if enough of the particular hormone is given, the results, by and large, are about the same with cortisone as with ACTH.

Treponemal Immobilizing Antibody and the Treponemal Immobilization Test

The standard serological tests for syphilis in use at the present time enable us to detect syphilitic infection with a relatively high degree of accuracy. These tests measure the presence of Wassermann antibody or "reagin" developed in the blood, and sometimes the spinal fluid, during the course of syphilitic infections. This Wassermann-type antibody, however, is not a specific antibody—for it occurs, not only in treponemal infections but also in certain other diseases such as infectious mononucleosis, leprosy, malaria, systemic lupus erythematosus, etc. Indeed, it sometimes is found in small amounts in perfectly normal individuals.

Recently a method has been devised for demonstrating the presence

of an antibody in the sera of syphilitic persons which is distinct from the Wassermann-type antibody and which has the specific ability to immobilize virulent Treponema pallidum in vitro.[1] This immobilizing antibody is present in human sera shortly after the onset of syphilitic infection. It is associated with the globulin fraction of the serum, requires complement for its action, is relatively heat stable, and apparently is spirocheticidal. In syphilitic patients the immobilizing antibody develops during the early stages of the disease (sometimes rather slowly) and the percentage of positive immobilization tests increases with the duration of the infection. Since the treponemal immobilizing antibody does not occur in the sera of normal individuals or those with other diseases, *except yaws and pinta*, the test appears to afford a reliable method for detecting biologic false-positive reactors. However, at the present time the technique of the T. P. I. test is so cumbersome, time-consuming and expensive, that its use must necessarily be limited to a few research laboratories.

The technique used for the detection and measurement of the immobilizing antibody employs virulent T. pallidum as the antigen. The organisms are extracted from rabbit testicular syphilomas in a special basal medium under anaerobic conditions. The suspension obtained is mixed with guinea pig complement and dilutions of the serum to be tested. After sixteen to eighteen hours of anaerobic incubation at 35° C the percentage of immobilized spirochetes is determined by examination under the dark-field microscope. The test is interpreted as positive if the difference in motility determinations between the complement-containing sample and the complement-free control exceeds 50 per cent. Since the organisms are either fully active or quite nonmotile under these conditions, the differentiation of positive and negative tests is usually quite clear-cut. Non-specific immobilization may occur if penicillin or other spirocheticidal agents are present in the serum or if the spirochetes used in the test are taken from rabbit syphilomas that are so old that they have become sensitized to antibody already developed in the infected rabbit itself. Non-specific immobilization may also occur if the blood serum has been collected in tubes that are not chemically clean.

Although the number of sera tested by this method is still relatively small, the results indicate that the detection of treponemal immobilizing antibody is an accurate test for the diagnosis of human syphilis. The im-

mobilizing substance appears in the serum during the primary and secondary stages of syphilitic infection and continues to be present during the remainder of the disease if early and adequate treatment is not given. This is in contrast to the spontaneous decline in the Wassermann-type reagin which may occur in some untreated cases. On the other hand, if adequate penicillin treatment is given in early syphilis, the level of immobilizing antibody will decline significantly over a period of months. In cases of latent or late syphilis, however, no such decline in immobilizing antibody can ordinarily be expected no matter how much antiluetic treatment is given. As already mentioned, no positive treponemal immobilization reactions have been obtained with sera from normal individuals or from patients with diseases other than syphilis—with the exception of yaws and pinta.

Studies on the Life Cycle of Treponema Pallidum

One of the more significant advances in the field of microbiology during the past few years has been the development of techniques which have permitted a better understanding of the life cycle of Treponema pallidum. DeLamater and his associates,[2] using specially stained preparations as well as the phase contrast microscope, have made a series of interesting and important observations on the occurrence of a complex life cycle in pathogenic forms of this microorganism.

These investigators have shown that the pathogenic T. pallidum, as it exists in the syphilitic rabbit testis, has two means of vegetative reproduction. One (and probably the most important) is by simple transverse division; the other is by the production of buds or gemmae. In transverse division, a spirochete about to divide, bends rapidly at one point, forming a sharp angle on itself. Then it lashes back and forth until a break occurs in the continuity of its cell body. After a short rest period the two parts begin to rotate in opposite directions and twist themselves apart. The production of buds may occur at any point along the spirochetal body and the buds may be single or multiple. In this type of reproduction the buds separate from the parent spirochete, remain free, and then form unispirochetal cysts. In each of these cysts a single spirochete develops, differentiates and finally emerges.

In addition, these investigators have also found that a more complex life cycle may occur in the pathogenic Treponema pallidum. In this, actively motile spirochetes come together in pairs or complex clusters

and appear to fuse. Then large multispirochetal cysts are formed, and in these, numerous organisms begin to develop. Later on the spirochetes emerge from the large cysts and go on to reproduce vegetatively by undergoing the type of transverse division and bud formation already described. Observations of this type, made by phase contrast microscopy, have now been confirmed by stained material. The results strongly suggest that in addition to vegetative reproduction by transverse division and by the production of buds, a complex life cycle occurs in pathogenic forms of Treponema pallidum.

Penicillin Treatment of Syphilis

Since the advent of penicillin, the treatment of syphilis, in all its stages, has become a relatively simple procedure. The accumulated data obtained from thousands of syphilitic patients of all types have now clearly established the superiority of treatment with penicillin alone in virtually all cases. Only rarely will supplemental measures such as heavy metal or fever therapy be necessary.

The introduction of the slowly absorbed crystalline procaine penicillin G in oil with 2 per cent aluminum monostearate has made it even easier to adopt a variety of schedules for the treatment of all types of the disease on an ambulatory basis. I believe that the most satisfactory and the most convenient form of treatment for all types of syphilis at the present time is that employing a slowly absorbed penicillin, intramuscularly, twice weekly until the desired total dosage has been reached. Moreover, there is an added advantage in using slowly absorbed penicillin over longer periods of time since we now know that, within limits, the longer the period taken to administer a given total dosage of penicillin, the more effective the therapy is. The reason for this is that Treponema pallidum, although it is susceptible to relatively low concentrations of penicillin, has a much longer killing time than most other organisms—indicating the necessity for maintaining adequate levels of penicillin in the tissues for a sufficient period of time.

A total dose of 4.8 to six million units for early syphilis and six to nine million units for latent and late benign syphilis will probably be sufficient and will certainly be as effective as any combination of heavy metal therapy used in the past.

For cardiovascular syphilis and all types of neurosyphilis the same type of penicillin, given twice weekly, to a total dosage of 12 to 18

million units is probably the treatment of choice. If necessary, repeated courses of treatment may be given after six months or so. In cardiovascular syphilis, many clinicians have discarded preparation with heavy metals before starting penicillin therapy and, in fact, start treatment on full doses of penicillin. Herxheimer reactions have not been common in cardiovascular syphilis treated with penicillin. Moreover, if such a reaction is to occur it will probably do so as readily when treatment is begun with small doses of penicillin as when full doses are used initially. In neurosyphilis, fever therapy is still used and may very well be advisable if the results from penicillin alone, either clinical or serologic, are unsatisfactory.

Penicillin, 600,000 units twice weekly for five weeks, given to the pregnant woman at the end of the first trimester will prevent congenital syphilis. If labor is imminent the penicillin may be given in daily doses. Even if it appears to be too late to prevent infection of the fetus, penicillin treatment may be very effective in "curing" such an infection in utero. Pregnant women who have already received adequate penicillin treatment for syphilis in the past need not be re-treated during subsequent pregnancies if the serologic tests have become negative or remain at a fixed low titer. In such cases, however, if there is any doubt whatsoever, it is safer to re-treat.

In early congenital cases, 20,000 units of slowly absorbed penicillin per pound of body weight twice weekly for four to five weeks is effective. In older children 600,000 units twice weekly for five weeks is usually recommended.

Reactions to penicillin-aluminum monostearate are less numerous than were the reactions to the older penicillin preparations. The fact that a patient develops urticaria or other manifestations of penicillin sensitivity during therapy does not mean that the sensitivity is permanent. Indeed, the evidence is that penicillin sensitivity is often rather transitory and many of these cases will tolerate penicillin within a few weeks after the reaction has subsided. If not, then penicillin "O' or even other antibiotics such as Aureomycin, 3 to 4 grams daily for two to three weeks, may be tried.

Treatment of the So-called Minor Venereal Diseases

While I am on the subject of venereal disease, it may be worthwhile to mention briefly the use of the newer antibiotics in the treatment of

the so-called minor venereal infections—lymphogranuloma venereum, granuloma inguinale and chancroid.

Granuloma inguinale may be treated with streptomycin two grams daily for three weeks or with Aureomycin, Terramycin or chloramphenicol two to three grams daily for three weeks. I still believe that streptomycin is perhaps the most effective agent in this disease although one sometimes encounters cases which are resistant to this drug and ultimately respond better to one of the other agents. Recently dihydrostreptomycin has been used with good results but I am not in favor of its use for any prolonged period of time because of the toxicity it has shown for the hearing apparatus. Streptomycin may cause disturbing vestibular damage but this is something that the patient can compensate for. The sudden deafness sometimes encountered after prolonged dihydro-streptomycin treatment is apt to be permanent and this is something that one cannot compensate for.

Lymphogranuloma venereum in its early stages—with local ulcer formation and buboes—does not respond very well to any of the antibiotics. At this stage of the disease, sulfadiazine, four grams daily for about three weeks, is probably the best treatment available. In the later manifestations, that is, cases with proctitis or draining sinuses, etc. Aureomycin is probably the treatment of choice. A dose of 2 grams daily must sometimes be continued for four to eight weeks before an effect is obtained. Although nothing much is said about it in the literature there is really nothing to prevent combined therapy with Aureomycin and sulfadiazine.

For the treatment of chancroid, streptomycin, Aureomycin and chloramphenicol are all effective when given in doses of two grams daily for seven to ten days. Sulfadiazine is also very effective and actually is still about as good a method of treatment as any.

The L. E. Phenomenon in Systemic Lupus Erythematosus

A laboratory test which has proved to be a valuable and accurate aid in the diagnosis of systemic lupus erythematosus is now available. This test is particularly useful when the absence of a typical skin eruption makes the diagnosis otherwise difficult.

In 1948 Hargraves and his associates[3] noted the presence of peculiar cells in the bone marrow of patients with active systemic lupus. They

called these "L.E." cells and showed that their occurrence was the result of a clumping of mature polymorphonuclear leukocytes which then engulfed amorphous, homogeneously-staining, basophilic material to give them a characteristic appearance. Later on it was shown that these cells may also be found in the buffy coat of the peripheral blood from patients with systemic lupus erythematosus.

It then became apparent that the factor responsible for the agglutination of the polymorphonuclear leukocytes and formation of the L.E. cells in the blood and bone marrow is contained in the gamma globulin fraction of the plasma in systemic lupus.[4] When mixed with normal bone marrow, or even normal buffy coat preparations, the plasma or serum of patients with systemic lupus will induce the formation of rosettes of leukocytes and characteristic inclusion-containing L.E. cells. This finding has become the basis for the technique now widely used for demonstrating the presence of the L.E. factor in the blood of patients suspected of having systemic lupus. One merely mixes the suspected plasma or serum with normal heparinized marrow or whole blood and, after waiting thirty minutes, spins the mixture in the centrifuge and prepares Wright's stained smears of the buffy coat. If the suspected plasma or serum contains the L.E. factor, rosettes of clumped leukocytes and L.E. cells will be seen. As a matter of fact, the clumping of leukocytes to form rosettes is sufficient for the diagnosis and one does not have to find the typical L.E. cell itself.

Thus far this phenomenon has been observed only during the active phases of systemic lupus. The patient need not be acutely ill, however, to show a positive plasma L.E. test. It disappears during remissions and is not found in such conditions as chronic discoid lupus erythematosus, multiple myeloma, rheumatoid arthritis, scleroderma, dermatomyositis or periarteritis nodosa. The test has become a valuable diagnostic aid in systemic lupus and has shown how protean and atypical this disease may be. For example, cases of atypical rheumatism or arthritis, some of them with a past history of epilepsy or positive serologic tests for syphilis, have been shown to be, in reality, cases of systemic lupus erythematosus.

Unsaturated Compounds in Sebum and Hair Loss

Recent experimental work has shown that certain naturally occurring compounds having unsaturated double bond carbon atom linkages are able to inactivate or interfere with the metabolism of the free

sulfhydryl groups of glutathione and human epidermis.[5] When such unsaturated compounds are applied to the skin of experimental animals they cause a localized type of hair loss, presumably by interfering with the function of sulfhydryl compounds which are necessary for normal keratinization and hair growth. After such applications, the sheath cells of the hair follicles undergo degeneration and hair loss results without any accompanying signs of inflammation.

Three naturally-occurring compounds which have unsaturated —C—C— groupings and which regularly exhibit this depilatory action—squalene, oleic acid, and linoleic acid—are normal components of human sebum. All three of these substances can inactivate sulfhydryl compounds and can cause hair loss in animals. The implications are that these normal constituents of sebum may be factors in the production of some types of human baldness—but so far there is no experimental evidence in humans to support this.

Actually when human sebum (obtained by extracting the hair of children and adult males with ether) is applied to the skin of rabbits, hair loss occurs. This sebum will inactivate sulfhydryl compounds in vitro and the general theory now advanced is that the unsaturated compounds found in sebum may play an important role in disturbances of hair growth and keratinization. It is the first instance in which a substance excreted onto the normal skin has been shown to influence the growth of hair and it may be that this finding offers a chemical clue to the etiology of human baldness. In any event, it suggests that sebum can no longer be considered merely as an inert lubricating agent but that it must be regarded as a chemically active substance which influences the process of hair growth and keratinization.

These, then, are some of the advances that have been made in dermatology during the past few years. There are several additional developments which deserve discussion but which have been omitted because of limitations of time. These include the basic experimental studies which have done so much to explain the phenomenon of poral closure and the sweat retention syndrome—and which have shown the importance of these mechanisms in anhidrosis, miliaria and even pustular eruptions of the skin. The newer knowledge of tyrosinase activity in human skin and the role it plays in melanin formation; recently developed histochemical methods and their applications to dermatologic problems; the use of some of the newer antibiotics, particularly neomy-

cin, bacitracin and polymyxin B in infectious dermatoses—these are some of the other topics which certainly would merit full discussion if time permitted.

REFERENCES

1. Nelson, R. A., Jr. and Mayer, M. M. Immobilization of Treponema pallidum *in vitro* by antibody produced in syphilitic infection, *J. exp. Med. 89*:369-93, 1949.
2. DeLamater, E. D., Wiggall, R. H. and Haanes, M. Studies on the life cycle of spirochetes, *J. exp. Med. 92*:239-52, 1950.
3. Hargraves, M. M., Richmond, H. and Morton, R. Presentation of two bone marrow elements: the "Tart" cell and the "L.E." cell, *Proc. Mayo Clin. 23*: 25-28, 1948.
4. Haserick, J. R., Lewis, L. A. and Bortz, D. W. Blood factor in acute disseminated lupus erythematosus; determination of gamma globulin as specific plasma fraction, *Amer. J. med. Sci. 219*:660-63, 1950.
5. Flesch, P. and Hunt, M. Local depilatory action of some unsaturated compounds, *A. M. A. Arch. Derm. Syph. 65*:261-69, 1952.

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LOCAL ELECTROCORTICAL RESPONSES INDUCED BY TOPICAL APPLICATION OF ACETYLCHOLINE CHLORIDE TO HUMAN CEREBRAL CORTEX*

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STUDIES dealing with the electrocortical effects following topical application of acetylcholine chloride solutions to the cerebral cortex of animals have been reported previously.[1-9] The present investigation was undertaken in an attempt to determine for man the patterns of cerebral electrocortical response to acetylcholine chloride solutions similarly tested in a group of patients undergoing cerebral operations.

Method: Acetylcholine chloride solutions were freshly prepared at the time of operation in concentrations of 10 per cent or 20 per cent in physiological saline. Small cotton pledgets (1.5 mm. squares) were saturated with test solution and applied to exposed cerebral cortex for varying periods of time. In most instances, electrocorticograms were made with the pledgets in situ and with the aid of Marshall cortical electrodes and a Type III Grass six channel electroencephalograph machine. Cortex to cortex tracings were commonly employed with an interelectrode distance ranging from 0.8 to 5 centimeters. Some tracings were also made following the brief application to the cerebral cortex of small filter paper squares soaked in freshly prepared 2 per cent strychnine sulfate solution. All patients received Demerol,® morphine sulfate and atropine sulfate or scopolamine 1½ to 3 hours preoperatively and operation was usually performed under general anesthesia (nitrous oxide, pentothal-nitrous oxide, avertin-nitrous oxide).

Results: In six of the twelve patients tested, a profound change in the local electrocorticogram occurred after the topical application of 10 per cent or 20 per cent acetylcholine chloride solutions (Table I). In the twenty-nine tests made, a severe change in the electrocorticogram

* Presented February 19, 1952 before the Combined Meeting of The New York Neurological Society and Section of Neurology and Psychiatry at The New York Academy of Medicine.
Manuscript received for publication February, 1952.

TABLE I — INDICATING RESULTS FOLLOWING TOPICAL APPLICATION OF ACETYLCHOLINE CHLORIDE TO HUMAN CEREBRAL CORTEX

Case	*Clinical Diagnosis*	*Preoperative Medication*	*Anesthesia*	*Area of Application*	*Max. Duration of Application*	*No. of Applications*		*"Positive" Reactions*
						10%	*20%*	
(1) M.P.	Right Frontal Glioblastoma	Sodium Luminal & Atropine Sulfate	Nitrous oxide	Right Antero-Lateral Frontal	2 mins.	2	0	2
(2) R.B.	Left Frontal Metastatic Carcinoma	Atropine Sulfate	Pentothal & Nitrous oxide	Left Lateral Frontal	12 mins.	6	0	2
(3) J.R.	Multiple Metastatic Hypernephroma	Morphine Sulfate & Atropine Sulfate	Pentothal & Nitrous oxide	Left Lateral Frontal	17 mins.	2	0	1
(4) E.G.	Left Frontal Metastatic Carcinoma	Morphine Sulfate & Scopolamine	Local	Bilateral Posterior Parietal	24 mins.	0	4	1
(5) O.B.	Left Middle Cerebral Thrombosis	Demerol & Atropine Sulfate	Pentothal & Nitrous oxide	Bilateral Posterior Parietal	63 mins.	1	4	0
(6) R.G.	Psychomotor Epilepsy	Morphine Sulfate & Scopolamine	Nitrous oxide & Pentothal	Right Lateral Frontal	31 mins.	0	1	0
(7) S.K.	Left Cerebral Metastatic Carcinoma	Demerol & Atropine Sulfate	Nitrous oxide & Pentothal	Right Medial Frontal	10 mins.	1	2	0
(8) F.P.	Left Middle Cerebral Thrombosis	Morphine Sulfate & Atropine Sulfate	Avertin & Nitrous oxide	Right Medial Frontal	11½ mins.	0	1	1
(9) V.E.	Left Parietal Metastatic Carcinoma	None	Avertin & Nitrous oxide	Right Medial Frontal	27 mins.	0	1	0
(10) M.A.	Traumatic Encephalopathy	Demerol & Atropine Sulfate	Avertin & Nitrous oxide	Right Medial Frontal	45 mins.	0	2	0
(11) E.E.	Congenital Communicating Hydrocephalus	Demerol & Scopolamine	Avertin & Nitrous oxide	Right Medial Frontal	12 mins.	0	1	1
(12) A.E.	Focal Epilepsy	Demerol & Scopolamine	Pentothal & Nitrous oxide	Right Lateral Parietal	28 mins.	1	0	0

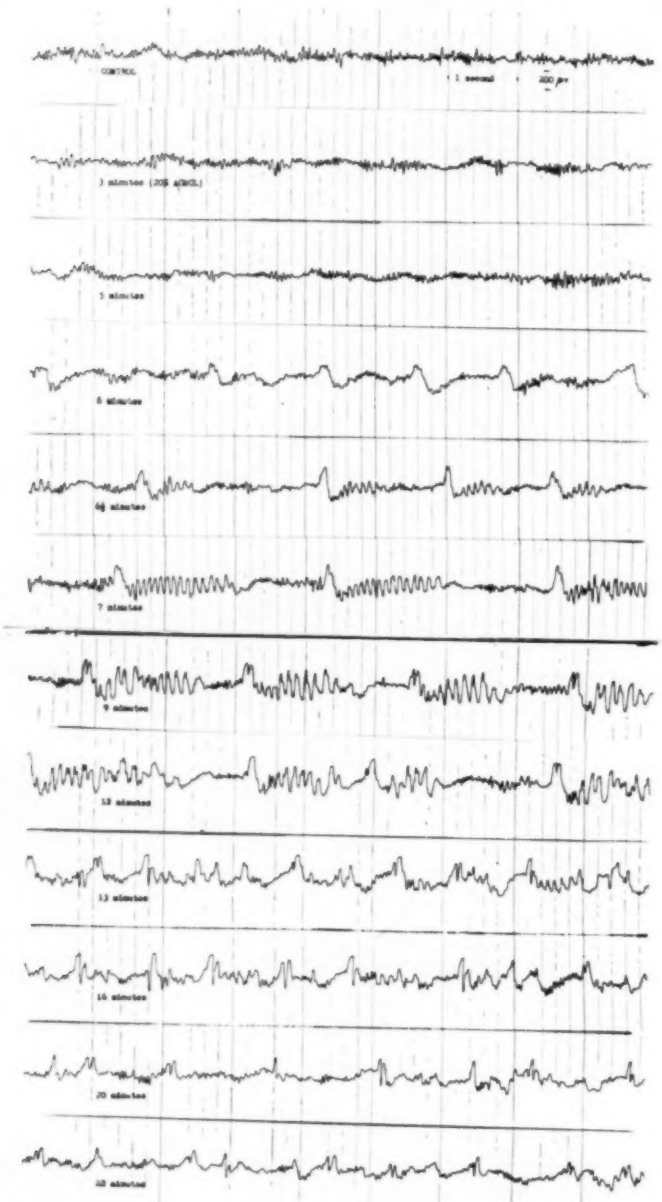

FIGURE 1—Serial electrocorticograms showing the local effects after application of 20% acetylcholine chloride for twelve minutes to a right frontal cortical area (Case 11).

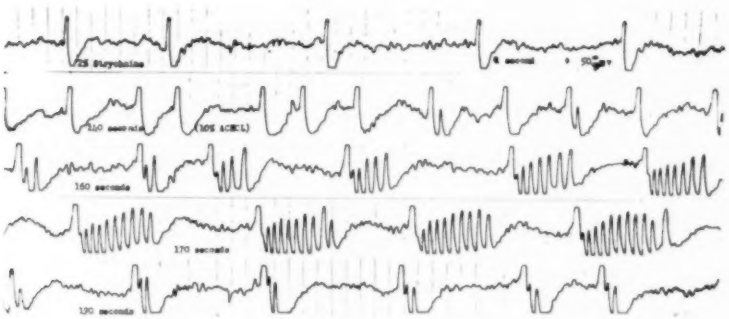

FIGURE 2—Serial electrocorticograms showing the local response of a strychninized right frontal cortical area after 10% acetylcholine chloride was applied for one minute (Case 1).

occurred in five of the nine times that the 10 per cent concentration was used and in three of the twenty times that the 20 per cent solution was employed.

There was usually a period of latency of six to eight minutes before significant electrocortical changes could be detected (Fig. 1). The first change noted was the presence of single negative waves of gradually increasing amplitude with a maximum of approximately 600 microvolts, and a frequency of one to two per second and a duration of 0.2 to 0.3 seconds. In the next phase of response, there occurred groups, clusters or spindles of increasing duration, in which high amplitude waves with a 5 to 8 per second frequency were dominant. With the 20 per cent acetylcholine chloride solution, the frequency within the spindles or groups was apt to center about 10 per second. The clusters, groups or spindles occurred in association with and immediately after the high amplitude single negative wave initially noted. In the ensuing phase, the initial high amplitude wave components were sometimes modified by the presence of an abrupt positive deflection so as to give the appearance of diphasic or triphasic spikes. Following the maximum response, the bursts of spindles, clusters or groups became less prominent, decreasing gradually in duration and amplitude. Thereafter the initial high amplitude negative waves and the spikes disappeared.

When a pledget of 10 per cent acetylcholine chloride solution was applied for one minute to a previously strychninized cortical area, a pronounced effect was noted (Fig. 2). Spikes immediately became very

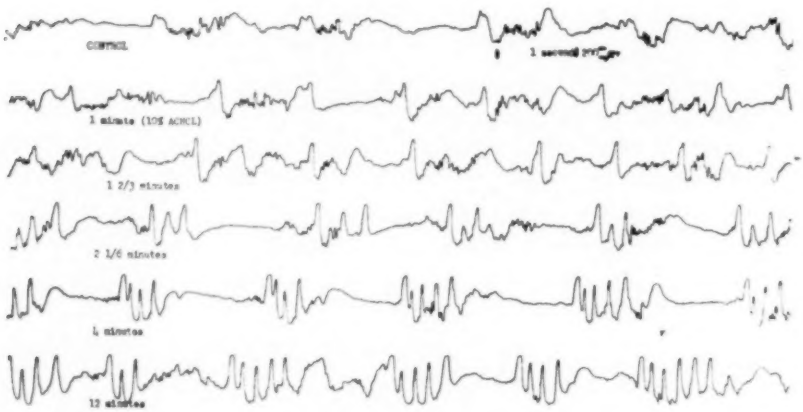

FIGURE 3—Serial electrocorticograms showing a decreased latency time and bursts of high amplitude 5 per second negative spikes following application of 10% acetylcholine chloride for twelve minutes to a previously responsive area (Case 2).

frequent and prominent and about one and a half minutes later high amplitude spindle bursts of 8 to 10 per second waves occurred immediately following the initial high amplitude negative spikes. This response reached its maximum three minutes after the acetylcholine chloride was applied and rapidly subsided thereafter in the ensuing one-half minute, the spindle bursts disappearing first. When a previously responsive cortical site was retested soon after the site had returned to its pre-test pattern, a greatly diminished latency in the onset of the new response sometimes occurred (Fig. 3).

Significant changes in the status of the patient and the cerebral cortex during and after the tests that could be attributed to the acetylcholine chloride were not noted.

Discussion: These findings indicate that significant alterations in the local electrocorticogram may occur several minutes after the topical application of 10 per cent or 20 per cent acetylcholine chloride solutions to human cerebral cortex. Although our series is small, there is a suggestion that the 10 per cent concentration may produce detectable changes more often than the 20 per cent concentration. Jordan, Badal and March[6] indicated that they obtained an "excitatory response" in 58 per cent of fifty-three applications of 10 per cent acetylcholine chloride in saline applied to the cat's cerebral cortex; our results with the use of

FIGURE 4—Representative electrocortical patterns following local application of 1% eserine and 0.5% acetylcholine to the cortex of the cat. A. Intact cortex; B. Thalamectomized hemisphere; C. Undercut cortex; 4. Isolated cortex. (Kristiansen, K. and Courtois, G. Electroencephalog. Clin. Neurophysiol. 1:265-71, 1949. Reproduced by permission.)

the 10 per cent solution (55 per cent) are in the same range. However, our overall results from use of both the 10 per cent and 20 per cent concentration are considerably lower (28 per cent).

We have not noted pronounced diminution of amplitude in the electrocorticogram in the period immediately after the test applications of acetylcholine chloride solutions. This is in contrast to some reports of the results in cats. Forster, Borkowski and McCarter[4] stated that in the cat, depression of electrical activity occurred locally within ten to forty seconds and then spread over the cortex in linear fashion, even in cases where no acetylcholine discharges occurred. This type of spreading depression encountered in the cat appears similar to that described by Leão[10] in the rabbit. Since Marshall and his workers[11-13] have indicated that factors such as dehydration and cooling are of extreme importance in the production of some spreading depressions, the absence of this finding in tracings made upon humans may be related to the vigorous efforts made to maintain appropriate hydration, temperature, electrolyte balance, etc. during surgical procedures in man. A species difference in reaction, possibly related to the comparatively higher

degree of cortical fissuration and the greater durability and complexity of the leptomeninges in man, may also be significant in this respect.

The maximum responses noted after the topical application of 10 per cent or 20 per cent acetylcholine chloride to human cerebral cortex resembled those described for animals after similar treatment with 10 per cent acetylcholine chloride or with eserine and 0.5 per cent concentration of acetylcholine chloride (Fig. 4). Facilitation of the acetylcholine chloride effect in man by previous strychninization is inferred from the prompt and pronounced response incurred under such circumstances. Forster and McCarter[5] noted that in cats strychninization of cortex followed by the application of acetylcholine chloride resulted in propagation of acetylcholine discharges to the area fired by strychnine, whereas ordinarily, acetylcholine discharges remained sharply localized to the region of application of the drug.

Since the average adult doses of atropine sulfate or scopolamine were routinely employed preoperatively, one would expect an adverse effect upon the response to a cholinergic substance such as acetylcholine chloride. However, it was felt that in most cases, the test period occurred after the presumed period of effectiveness of the preoperative medication. A distinct relationship of the response to the type and depth of anesthesia was not clearly demonstrated, and similar responses were noted under nitrous oxide, pentothal-nitrous oxide, avertin-nitrous oxide, and local anesthesia.

Significant cerebral pathological conditions were present in all cases, frequently in the area adjacent to the testing. In one instance (Case 8), however, a pronounced typical response occurred after the application of 20 per cent acetylcholine chloride solution to the cortex of a presumably intact cerebral hemisphere in a patient whose status was compatible with the clinical impression of a middle cerebral thrombosis of the opposite cerebral hemisphere. Altered leptomeningeal permeability was suggested as a factor especially in cases where gross physical changes in the pia were obvious.

A certain degree of control of the electrocortical response was possible by removal of the pledget from the cortex. Since we wished to avoid precipitation of frank motor convulsive phenomena, pledgets were always removed as soon as a relatively pronounced effect on the electrocorticogram was noted. Thereafter, the electrocortical response would begin to diminish in intensity and gradually disappear. An even

more pronounced electrocortical effect than any we have thus far encountered seems to be a definite probability in responsive cases through the use of more prolonged applications of the test substances. On some non-responsive occasions, however, the time or period of application appeared to be of minor importance; in one case 20 per cent acetylcholine chloride was applied continuously for sixty-three minutes without significant local electrocortical effect. The fact that some sites within a relatively small cortical area responded well and others did not, suggests the possibility of specific areal differences in the reaction to acetylcholine chloride. Since most of our test sites were within the frontal lobe, and because precise orientation was not always possible, an adequate basis for determining the presence or absence of a topographic pattern has not yet been attained.

Summary

1. Pronounced local changes in the human cerebral electrocorticogram could be induced by the topical application of acetylcholine chloride in 10 per cent or 20 per cent solutions.

2. In responsive cases, after a period of six to eight minutes, recurrent single, high amplitude one to two per second waves appeared.

3. Thereafter, recurrent spindles, groups or clusters of high amplitude 5 to 10 per second waves occurred in bursts immediately following the recurrent single high amplitude waves.

4. High amplitude diphasic and triphasic spike discharges were noted in the ensuing phase.

5. Recovery from the maximal response was characterized by the early diminution in duration and amplitude of the spindles, groups or clusters and was followed by the ultimate disappearance of the initial high amplitude negative waves and spikes.

6. Local early pronounced depression of electrical activity soon after the application of acetylcholine chloride solution was not noted.

7. Pretreatment of a cerebral cortical site with 2 per cent strychnine sulfate facilitated the response to 10 per cent acetylcholine chloride solution.

8. The influence of factors such as preoperative medication, anesthesia, cerebral pathological changes, leptomeningeal permeability, drug concentration, duration of application and site of application are considered.

(SEE REFERENCES ON FOLLOWING PAGE)

REFERENCES

1. Brenner, C. and Merritt, H. H. Effect of certain choline derivatives on electrical activity of the cortex, *Arch. Neurol. Psychiat. 48*:382-95, 1942.
2. Chatfield, P. O. and Dempsey, E. W. Some effects of prostigmine and acetylcholine on cortical potentials, *Amer. J. Physiol. 135*:633-40, 1942.
3. Forster, F. M. Action of acetylcholine on motor cortex; correlation of effects of acetylcholine and epilepsy, *Arch. Neurol. Psychiat. 54*:391-94, 1945.
4. Forster, F. M., Borkowski, W. J. and McCarter, R. H. Acetylcholine induced depression of cerebral cortical activity, *J. Neuropath. exp. Neurol. 5*:364-73, 1946.
5. Forster, F. M. and McCarter, R. H. Spread of acetylcholine induced electrical discharges of the cerebral cortex, *Amer. J. Physiol. 144*:168-73, 1945.
6. Jordan, W. K., Badal, D. W. and March, R. Interaction of effects of acetylcholine and adenosine triphosphate on electrical activity of cat cerebral cortex, *Arch. Neurol. Psychiat. 63*:766-73, 1950.
7. Kristiansen, K. and Courtois, G. Rhythmic electrical activity from isolated cerebral cortex. *Electroencephalog. clin. Neurophysiol. 1*:265-72, 1949.
8. Miller, F. R., Stavraky, C. W. and Woonton, G. A. Effects of eserine, acetylcholine and atropine on the electrocorticogram, *J. Neurophysiol. 3*:131-38, 1940.
9. Sjöstrand, T. Potential changes in the cerebral cortex of the rabbit arising from cellular activity and the transmission of impulses in the white matter, *J. Physiol. 90*:41*P*-43*P*, 1937.
10. Leão, A. A. P. Spreading depression of activity in the cerebral cortex, *J. Neurophysiol. 7*:359-90, 1944.
11. Marshall, W. H. The relation of dehydration of the brain to the spreading depression of Leão, *Electroencephalog. clin. Neurophysiol. 2*:177-85, 1950.
12. Marshall, W. H., Essig, C. F. and Dubroff, S. J. Essential factors involved in spreading cortical depression, *Amer. J. Physiol. 159*:579, 1949.
13. Marshall, W. H., Essig, C. F. and Dubroff, S. J. Relation of temperature of cerebral cortex to spreading depression of Leão, *J. Neurophysiol. 14*:153-66, 1951.

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AUDITORY THEORY: AN EXPERIMENTAL STUDY OF THE PLACE PRINCIPLE*

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THROUGHOUT the history of auditory theory the focus of attention has always been the place principle. This is the principle that every tone has its own place of action in the cochlea; and any tones that are distinguishable in pitch have different places of action. We are most familiar with this principle in its use in the Helmholtz resonance theory, where the determination of the specific place of action is made through a process of mechanical resonance.

A serious question is whether the place principle is adequate by itself to meet the requirements of pitch discrimination and of other phenomena of pitch perception. This question has been discussed elsewhere and the advantage is shown in combining this principle with the frequency principle for a general theory of hearing. However, this is not the question with which we are concerned at the present time. Granting the validity of the place principle in some measure, we are now concerned with the question of the form that this principle should take.

This question was raised early in the history of this subject as a result of dissatisfaction with resonance as the physical basis of the place principle. The dissatisfaction comes from a consideration of the limitations of resonance itself, and especially the manner of operation of resonance in the presence of damping. The damping of a resonator extends its effective range of response to many frequencies and thereby impairs its ability to respond selectively to any one frequency. Thus a resonance theory that admits heavy damping is in difficulty in accounting for our keen abilities of pitch discrimination. On the other hand, a resonator that is only lightly damped, like a tuning fork in air, will require an appreciable period of time to reach its maximum of vibration

* Presented to the Section on Otolaryngology of The New York Academy of Medicine, January 16, 1952.
From the Princeton Psychological Laboratory.
Manuscript received for publication February 1952.
This investigation was aided by a contract with the Office of Naval Research (N6-onr-270, T. O. 3, Project NR 140-322) and by Higgins funds allotted to Princeton University.

in response to some impressed tone and will likewise require time to die down to zero after this impressed tone is removed. A resonance theory that admits such light damping is in difficulty in accounting for our ability in distinguishing tones that follow one another quickly in time, as they do in speech and rapid passages of music. Thus we have a dilemma in which pitch discrimination calls for light damping and the differentiation of successive sounds calls for heavy damping; and the demands are such that no intermediate compromise of characteristics will satisfy them. Here is a very serious difficulty for a resonance theory.

A consideration of this difficulty has led to the search for a form of physical action other than resonance on which to base the place principle. Such a new basis has been found in the conception of traveling waves.

The term "traveling waves" is used here in a particular sense. All sound waves travel through media of all kinds; but we are concerned with this travel under rather special conditions, those provided by a flexible solid or semi-solid like a membrane immersed in a fluid. A fairly good analogy is provided by the waves produced in a rope whose one end is held in the hand and given a quick flip. A wave starts at the hand and moves progressively along the rope. If the rope is laid loosely along the ground the movement is slow and the wave quickly dies away to zero. If the rope is anchored at its farther end and stretched out the movement is more rapid and the wave proceeds a greater distance before it disappears. Thus the particular conditions in and about the rope determine the nature of the traveling wave. Now for the rope let us substitute the basilar membrane of the cochlea and for the hand to set it in motion let us substitute the stapes acting by way of the cochlear fluid. The stapes moves inward, pushes upon the adjacent fluid, and causes a displacement of the most basal portion of the basilar membrane. This displacement then proceeds as a wave toward the apex of the cochlea. An outward movement of the stapes initiates another displacement, contrary in direction to the first, and this wave likewise moves up the cochlea. So a succession of stapedial oscillations causes a series of waves to travel along the cochlea.

There are many particular theories regarding these waves and the particular patterns of motion that they display. The theories differ in detail according to the assumptions made as to the determining conditions: the influence upon the motion accorded to the mass, stiffness, and

damping characteristics of the basilar membrane and the surrounding fluid. The theories differ also as to what features of the response pattern are important in bringing about the final stimulation of nerve endings. We are not concerned with these individual details at this time but only with the general conception. We are content at present to contemplate certain features that are common to all formulations of the traveling wave theories, as follows:

1. The wave proceeds up the cochlea, changing in amplitude as it goes. Typically, the amplitude is said to rise for a time, to attain a maximum, and then to fall rapidly to zero.

2. Tones of different frequencies cause waves that rise at different rates and attain their maximums at different places before falling to zero. High tones rise rapidly, attain their maximums in the basal region of the cochlea, and expire there. Low tones proceed farther up the cochlea. All tones thus have their effects distributed over the cochlea in a manner that varies systematically with frequency. The requirements of the place principle are thereby satisfied.

3. The wave progresses along the cochlea at a relatively slow rate. This low speed of propagation is essential to certain forms of traveling wave theories where two or more waves must exist simultaneously in the cochlea. It is not theoretically demanded by others, yet even in these the particular assumptions made in their development lead to this result. The speeds assumed vary greatly from 5 cm. per sec. to 415 meters per sec. with a mean figure around 30 meters per sec. These values are small with respect to the speed of sound in a free body of water; the speed as calculated for sea water at body temperature is 1563 meters per sec.

We have carried out a series of experiments to test these basic assumptions of the traveling wave theory. The experiments were carried out on anesthetized cats by use of the electrical potentials of the cochlea. These potentials, as is well known, represent the activities of the inner ear, and more specifically, according to abundant evidence, the activities of the hair cells of the organ of Corti. With certain exceptions, to be noted presently, the potentials were recorded in the usual manner with an electrode on the round window membrane.

We stimulated these ears in two ways. One means of stimulation was the ordinary one, with an aerial sound introduced by a tube into the external auditory meatus and thus reaching the cochlea by way of

the ossicular chain and the oval window. The other means of stimulation was by way of a small hole drilled through the cochlear wall in the apical region. Sound was introduced into this hole by one of two methods, either as aerial sound through a small tube fitted over the hole or, more often, as mechanical vibrations of a needle inserted into the hole. The needle was made to fit the hole like a piston in a cylinder and exerted alternating pressures upon the cochlear contents when driven by a crystal vibrator. These two variations of the apical stimulation gave identical results and will not be distinguished hereafter.

In the two forms of stimulation, that by the usual oval window route and that by way of a hole in the apex of the cochlea, we used the same tonal frequency from a single oscillator. A divider network delivered the oscillator output to two control channels in which the tones were independently varied in intensity. Provision was made also for complete control of the phase relation between the two stimulating channels over a range of 0 to 360°. The range of frequencies was from 100 to 15,000 cycles per sec.

The experimental procedure consisted of stimulating at the two ends of the cochlea simultaneously and observing the resulting cochlear potentials. The results of such stimulation can be stated very simply: the potentials at all times represent a vector sum of the potentials obtained from the two stimuli acting separately.

The following simplified form of the procedure is a little easier to follow and was found advantageous for further exploration and for a long series of control tests. One stimulus was applied by itself and the intensity was adjusted so as to obtain some standard amount of response, say 10 microvolts, and then this stimulus was removed and the other applied separately and adjusted for the same amount of response. The two stimuli were then turned on together and the phase relation of the two varied continuously over a range of 360°. It was found that at a certain phase relation, which is not known absolutely and is of no particular interest at present, the two stimuli combine their effects to produce a response just double that of either acting alone. As the phase is altered from this relation the response falls continuously in magnitude until at a point 180° from this relation it becomes zero. This type of summation has been found for all tones of the audible range.

It is possible to show that this summation takes place in the fluid pathways of the cochlea by which the sounds reach the sensory cells or

in the sensory cells themselves and not in the conductive paths by which the potentials reach the electrodes. The evidence is that after conditions have been established for a certain summation of response with the electrode in one position the electrode may be moved to a new position without significantly altering the form of the summation. For this test a needle electrode was used. It was first placed on the basal end of the cochlea, the usual adjustments were made in intensity and phase for a cancellation of response, and then the electrode was moved to a new position. For all the low and intermediate tones, no new adjustments were necessary to maintain the cancellation. For the high tones, those above about 5000 cycles, some readjustments were required, but even at 10,000 cycles the phase changes were small in relation to a wave period. These readjustments were necessary for the high tones because the speed of conduction through the cochlea is not infinitely great; this conduction takes time, and even though the time is very short it becomes measurable in relation to the wave period of high tones.

These observations signify that the two stimuli reach the same sensory cells, reach them practically simultaneously, and affect them to the same degree.

It is necessary to conclude that every sound, whether applied at the base of the cochlea or at the apex, spreads over the whole cochlea at high speed and without appreciable attenuation. This is true of all frequencies alike. Thus the basic assumptions of the traveling wave theories are not supported. The speed of conduction through the cochlea is probably of the order of the transmission of sound through open water.

The fact, as indicated here, that any given sound wave reaches every part of the cochlea practically simultaneously does not demand that the movement of all parts of the basilar membrane shall likewise be simultaneous. These parts will move with time constants that are determined by their local characteristics.

The evidence of this experiment is not merely negative. In its denial of the traveling wave concept the evidence points directly to a local action type of theory. We must look to local conditions in the cochlea for the anatomical basis of the place principle and for whatever specificity of behavior the cochlea exhibits.

NEW YORK PATHOLOGICAL SOCIETY

*Abstracts of Papers**

Presented at the Meeting, March 27, 1952 at The New York Academy of Medicine

A General Theory of Bone Tumors

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Although pathologists attempt to classify tumors into readily separable groups on the basis of morphology and behavior, many tumors do not completely conform to their classification. To classify bone tumors with descriptive fidelity would frequently necessitate multi-hyphenated terms because of "impure" tumors which exhibit the traits of several categories. In clinical practice it is convenient to think of the major bone tumors as falling into ten basic types, and to label individual specimens, according to the concept of "predominant cell type," with that one of the following terms which gives the best approximation.

Chondrosarcoma
"Chondroblastoma" (Codman's tumor)
Osteosarcoma
"Osteoblastoma" (parosteal osteoma)
(juxtacortical sarcoma)
Giant cell tumor (osteoclastoma)
"Osteolytic sarcoma"
(pleomorphic sarcoma)
Fibrosarcoma (medullary)
Reticulum cell sarcoma
Ewing tumor
Multiple myeloma

Underlying these approximations is a range of cell types and organoid patterns common to all of the categories. Furthermore, they all share in a common biochemistry and cytology of matrix formation, and they conform to regional variations in the structure of normal bones and of the skeleton. And when the tumors are analyzed with respect to space, time, and quantity—where, when, and how often they occur—it would appear that they behave in an orderly and predictable manner.

1. *Histology of the Tumors.* Each of these ten types is a distinct clinical, radiologic, and anatomic complex named for a characteristic and predominant cell type that is usually recognized by its products; e.g., osteosarcoma and chondrosarcoma are so named because they produce bone and cartilage respectively. The chondroblastoma of Jaffe (Codman's "epiphyseal chondromatous giant cell tumor") is a relatively mature tumor made up of cells that approach the appearance and behavior of normal chondroblasts. "Osteoblastoma" would be the homologous term for the tumor of osteoblasts called "parosteal osteoma" by Geschickter and Copeland (Jaffe's "juxtacortical osteosarcoma"). Both "blastomas" are slow growing and sufficiently mature in appearance to be mistaken at times for non-neoplastic hyperplasias or reparative patterns.

The large cell for which the giant cell tumor is named shows the same phosphatase

* Manuscript received for publication March 1952.

activity as the osteoclast, is likewise free of phagocytic activity, and may metastasize to the lung in malignant forms of this tumor. Hence, the giant cells are regarded as neoplastic osteoclasts. And because transitional forms between the giant cells and the so-called "stroma cells" are demonstrable, the latter are regarded as mononuclear predecessors of the multinucleated forms.

"Osteolytic sarcoma" is the term used to designate a primary tumor that destroys bone and is made up of extremely pleomorphic cells that generally fail to produce any matrix. Whole bone sections of these tumors have on several occasions shown the characteristic cell types merging into areas typical of malignant and even of benign giant cell tumor; therefore we regard it as an extremely malignant derivative of the giant cell tumor.

All of the fibrosarcomas in our material are medullary in origin; those thought to be periosteal fibrosarcomas generally proved to be primary in the soft tissue adjacent to, but not part of, the bone.

When some 1500 tumors in the Registry of Orthopedic Pathology were classified and analyzed, a very wide range of cell types was noted in each category. For example, within the group of typical chondrosarcomas individual fields were morphologically indistinguishable from osteosarcoma, Codman's tumor, parosteal sarcoma, giant cell tumor, osteolytic sarcoma, fibrosarcoma, reticulum cell sarcoma, Ewing tumor, and even myeloma. A similar range of cell types may be found in every class of tumor; the mononuclear "stroma cells" of giant cell tumors undergoing sarcomatous transformation are quite likely to lay down a chondroid matrix; in reticulum cell sarcomas, collagen, fibrocartilage, and osteoid material may form in condensations of the abundant reticulum.

While the Ewing tumor is usually thought of as monotonous sheets of closely packed, generally round nuclei, with scarcely any visible cytoplasm, Ewing himself illustrated cells with considerable water-clear cytoplasm. When these suggestions of cytoplasmic activity were investigated, we found them to result in extracellular mucoid material which occasionally developed into patches of typical cartilage or into slender spicules of chondro-osteoid material, birefringent in polarized light and occasionally calcified.

Likewise, myeloma cells, in addition to amyloid, Bence-Jones protein, and a lipoprotein associated with anticomplementary Wassermann reactions, were found to produce an abundance of reticulum, patches of mucoid material, and occasional optically active chondro-osteoid bands that sometimes calcify. Furthermore, the appearance of myeloma cells and their reaction to methyl green pyronine are as closely duplicated by the normal osteoblasts of undecalcified embryonic bone as they are by non-neoplastic plasma cells.

Therefore, at least some of the osseous reticulum cell sarcomas, Ewing tumors, and multiple myelomas can produce matrices which are characteristic of skeletal tissue, and such behavior would seem to indicate that they belong among the skeletal neoplasms.

2. *Biochemical and Cytological Background.* The interpretation of these observations is dependent upon the known chemical properties of normal bone matrix. The organic component of both bone and cartilage is made up of a fiber protein of the reticulum-collagen series and a mucoid glycoprotein of the mucopolysaccharide series, with the fiber protein predominant in bone and the glycoprotein predominant in cartilage. The fiber protein has a special configuration of particular amino acids and a characteristic pattern on electron microscopy and on x-ray diffraction. The mucopolysaccharide consists of long chains of cyclical hexose derivatives, with sulfate and amino side radicals. The fiber protein and the polysaccharide can combine stoicheiometrically because of similar periodicity and strategically placed active side radicals to produce a single new substance, osteoid, which is able to calcify after molecular rearrangement and loss of water.

The collagen and polysaccharide are the products of osteoblasts and of chondroblasts. Collagen is probably synthesized from polypeptides and amino acids in a protein-rich tissue fluid by the interface activity of the cell "membrane," and is thus

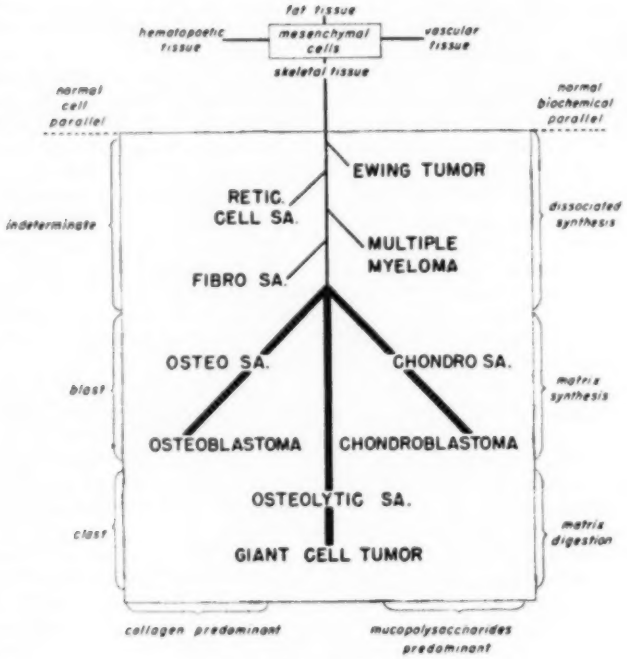

Fig. 1

an extracellular product. The mucopolysaccharide, on the other hand, appears to be produced within the cytoplasm and is secreted onto the developing collagen. Ordinarily it takes about ten days for osteoblasts to produce calcified bone, but only eight hours for an osteoclast to digest and destroy it enzymatically, a time differential of considerable importance when balancing osteoblastic against osteoclastic activity.

The relationship between osteoblasts and osteoclasts is particularly well displayed in the egg laying cycle of birds; calcium is stored by filling the marrow cavities with bone while the ovum is maturing and is released by clearing out the extra bone for the eggshell when the egg enters the shell sac. When this cycle is telescoped into twenty hours (as in the pigeon) it appears that the osteoblast and the osteoclast are the same cell, since they rapidly change from one morphologic type and function to the other, without intervening cell division. Hence the names given to the cells merely designate varying forms and functions of the same cell.

3. *Interpretation of Relationship of Tumor Types.* When the full range of cell types in each of the ten categories of tumors is considered against this background, a precise form of kinship may be postulated (see diagram), based upon the degree to which each tumor type duplicates the normal organic chemistry of matrix production. The tumors in the upper third represent incomplete patterns of organic synthesis, while those of the middle third regularly produce abundant skeletal matrix. On one side are those tumors of predominantly collagenic structure, and on the other, those of

predominantly glycoprotein makeup. Tumors of the lower third consist of cells which attempt to duplicate osteoclastic activity.

This formulation suggests that abortive attempts at organic synthesis may occur in the Ewing tumor and permit the escape of polypeptides, proteoses, or peptones into the circulation to produce fever, leukocytosis, and elevation of the sedimentation rate—a problem for chromatographic investigation of blood and urine.

Similarly the amyloid, Bence-Jones protein, and other abnormal organic products of multiple myeloma may be complex proteins and lipids resulting from conjugation with the products of abortive mucopolysaccharide synthesis—and polysaccharide studies of blood and urine may clarify such relationships.

Ordinarily the mononuclear cells of the giant cell tumor omit the phase of synthesis and develop directly into multinucleated tumor osteoclasts. But their latent ability to behave as "blast" cells is unmasked by their tendency to produce cartilage in giant cell tumors which are undergoing malignant transformation. The same potential on the part of the mononuclear cells is evidenced by the foci of cartilage to be found in many benign giant cell tumors of the hands and feet, in the rare enchondromatous giant cell tumors of the metaphyses of long bones, and in the epiphyseal chondroblastoma or Codman tumor. Thus, the neoplasms demonstrate the same relationship between "blast" cells and "clast" cells that obtains in normal bone.

4. *Skeletal Metabolic Fields.* Bone is more than a tissue; it is an organ with special and varying functions in different portions not only of the skeleton but also of the separate bones. There is a metabolic gradient within each individual bone as evidenced by variations in thermocouple readings, circulatory rates, capillary and sinusoidal dilatation, mitotic activity, relative proportions of osteoblasts to osteoclasts, rates of organic matrix synthesis, Ca/P ratios, Ca/N ratios, P/N ratios, carbonate/phosphate ratios, rates of exchange of radioactive tracers, and madder feeding, and by the variations of these data with age and with disease. The gradient is a low level in the epiphysis and minimal in the midshaft, while it is high in the metaphyseal regions and maximal in the metaphysis of the more rapidly growing end.

Once the bone has gained sufficient size for the metabolic gradient to be spread out in space, it can be correlated with fields of cell activity (Fig. 2A). In childhood, the epiphysis is only moderately active with a limited and rather precarious blood supply. Not until the growth plate closes does collateral circulation develop from the abundant metaphyseal blood supply. The essentially bloodless growth plate first synthesizes, then resorbs cartilage matrix, simultaneously inducing a narrow zone of intense osteoblastic activity as a result of the phase of cartilage maturation. The subjacent half of the metaphysis (3) is a field of overbalancing osteoclastic activity as primary trabeculae are resorbed and the original cortical silhouette is cut back in remodelling the broad diameter of the growth plate to that of the slender shaft. The diaphyseal half of the metaphysis (4) is a region of compensating preponderance of osteoblastic activity as bone is reconstituted, particularly along the endosteal surface of the cortex. Activity in the diaphysis (5) is largely periosteal in location while endosteal activity and cancellous bone in the marrow cavity disappear by osteoclasis.

During early adolescence, as circumferential growth of the shaft nears completion, the conversion of lamellar bone to Haversian systems begins. After the epiphyseal growth plate closes, the stress-strain cancellous trabeculae (which are present as two independent systems on either side of the plate before closure), are resorbed and simultaneously reconstituted into a single new system of major weight-transmitting trabeculae.

5. *Place of Origin of Tumors.* When the very small and presumably early tumors of each category are analyzed, it becomes apparent that there are preferential sites of origin within each bone. In general, a particular tumor of a given cell type usually arises in that field where the homologous normal cells are most active, as illustrated in Fig. 2B. For example, giant cell tumors,

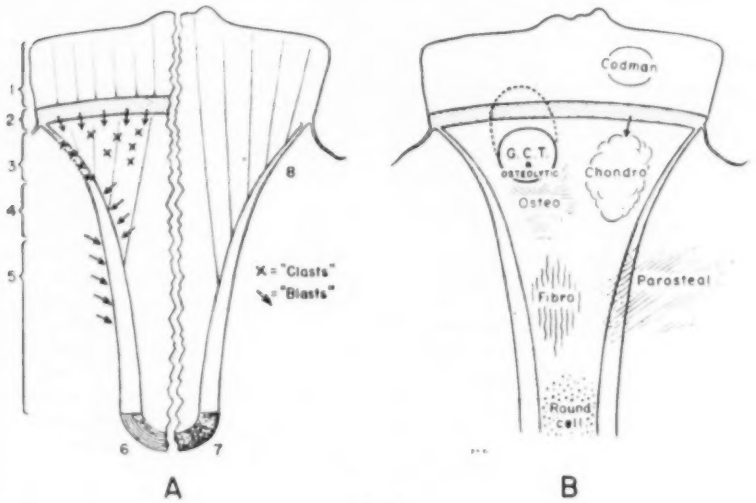

Fig. 2

when small or when seen before the epiphyseal plate closes, are always located in the osteoclastic field of the metaphysis. After the plate disappears they spread, with reconstructive activity, into the epiphysis. As might be anticipated, osteolytic sarcomas have an identical distribution. Fibrosarcomas arise where cancellous bone is disappearing from the medullary cavity. The three round cell sarcomas (myeloma, Ewing's, reticulum cell) develop in the bone-free marrow cavity of the mid-shaft. The parosteal sarcoma arises from the periosteal surface at the junction of the metaphysis and shaft, in the field of predominant periosteal activity. Though usually a tumor of the surface of the cortex, it may occasionally arise within the bone and the internal portion will then appear as a low grade fibrosarcoma. Thus a single tumor may have cellular components which characterize two different fields. Similarly, an occasional sarcoma of adolescence may present as a "double" tumor, appearing as a giant cell tumor in the metaphysis and as an osteosarcoma where it extends into the shaft of the bone.

These regional variations suggest that the character of the tumor may be determined by the metabolic field in which it arises. Such speculations are encouraged by the striking change in cellular make-up of many tumors after they break out of the bone into the soft tissues—as if escaping the control of local field influences. A further suggestion comes from the variation of tumor patterns in different portions of the skeleton. The metabolic gradient of the bones of each limb drops as one progresses distally, and enchondromas, for example, show a parallel decreasing incidence of sarcomatous transformation. (In this respect, the Codman tumor in long bones behaves as if the epiphyseal metabolic level approximated that of the phalanges.)

6. *Time of Origin of Tumors.* The three forms of round cell sarcomas arise in the same general location but in different age groups: childhood-adolescence for Ewing tumor, adulthood for reticulum cell sarcoma, and middle and old age for myeloma. Borderline tumors appear in the third and fourth decade; it may be that the changing metabolic activity of bone with increasing

age may influence the character of the cells comprising the tumor.

Apart from the three round cell tumors, the majority of bone tumors develop in late adolescence—the 15 to 25 year age-range. This is the time of the last growth spurt and maximal reconstructive activity of both cortical and cancellous bone, and it is the period when the various tumors are seen in their most characteristic form. Giant cell tumors, osteosarcomas, and chondrosarcomas predominate (and, if one avoids hyphenated terms, naming the tumors for the quantitatively predominant component, chondrosarcomas are more common them osteosarcomas).

The highly malignant bone tumors of childhood show extensive areas of undifferentiated round cells, so that the osteosarcomas in part resemble Ewing tumors. In mid-adult life, however, the same neoplasms tend to be much slower growing and more mature in appearance. In the fourth decade the usual polyhedral mononuclear "stroma cells" of the giant cell tumor frequently assume spindle patterns to look like fibroblasts, or fill with fat to appear as xanthoma cells. Parosteal sarcomas ("osteoblastoma") and fibrosarcomas, with their notably better prognosis, are largely tumors of this period. Furthermore, there are some periosteal chondrosarcomas of the shaft and a group of osteosarcomas of the midshaft of major long bones that develop in the fourth decade, which are very slow growing and well differentiated, and approximate in prognosis the parosteal sarcoma and fibrosarcoma.

7. *Quantitative Factors in Tumor Incidence.* Although the majority of bone tumors develop during the period of maximal bone reconstruction, it is important also to recall that most of them occur in the longest bones (humerus, tibia and femur) which show the most growth and reconstruction. Furthermore, the larger number occur in that end of each of these bones where growth is greatest (shoulder and knee regions). This suggests a relationship between the number of tumors and the amount of cell activity, a relationship implicit in evidence of an antecedent benign fibrous lesion in 25 per cent of the fibrosarcomas, and in the incidence of chondrosarcomas developing from enchondromas and osteochondromas. The propensity for excessive cellular proliferation to progress to neoplasia is further suggested by the occasional development of bone sarcomas in the actively proliferating margin of a bone infarct, an old osteomyelitic scar, or an old unresolved callus. Recently there has been a growing suspicion that pregnancy may enhance the activity of some bone tumors as might be expected from the additive effect of growth hormone, estrogens, and androgens on osteoblastic activity. Von Recklinghausen's generalized osteitis fibrosa cystica may be associated with true giant cell tumors as well as with the brown tumor of hyperparathyroidism. Finally, Paget's disease is notorious for its high incidence of osteosarcomas and giant cell tumors, and occasionally a peculiar double tumor of both osteoblasts and osteoclasts may be seen.

The underlying common factor would seem to be that diseases characterized by prolonged periods of excessive cell activity carry an increased hazard of neoplastic transformation of those cells.

Summary

Thus, an analysis of where, when, and how often bone tumors occur indicates that these neoplasms are not completely autonomous but are subject to the laws of field behavior of normal bone, which they may caricature, but cannot wholly escape.

The various categories of tumors represent abortive attempts at, or varying degrees of success in recapitulating the organic chemistry of production and destruction of skeletal matrices by the cytoplasmic activity of the cells.

The appearance of a particular tumor seems to be the result of the influence of the field forces upon the neoplastic cells and is manifested by a characteristic cytoplasmic activity which defines the tumor. Thus, the broad aspects of the biologic behavior of bone tumors are reflected in their morphology, and, conversely, their biology may be inferred from a detailed study of their morphology.

DISCUSSION

HENRY L. JAFFE: Dr. Johnson has conveyed to us, very interestingly, his conception of the bone tumors. How he can derive them all from the same basic cell and at the same time recognize that there are clinico-anatomic differences between the various bone tumor entities is the task of his theory to explain. In the first place, he lays great stress upon the fact that, along with the predominant tissue pattern presented by one of the given tumor entities, a specific lesion may show some tissue fields suggesting one or a number of the other clinico-anatomic tumor types. However, he overemphasizes this so-called histologic overlapping of the tissue patterns in the various tumor types, and, furthermore, he fails to note that, in a particular bone tumor, one may encounter tissue elements which are not the product of the actual tumor cells of the lesion at all. Nevertheless, Dr. Johnson is not diverted by this idea of overlapping tissue patterns when faced with the question of classification and of diagnosis directed toward treatment. He recognizes, as do all of us who deal with these matters, that, in applying a diagnosis to a particular tumor, one is guided by the dominant histologic tissue pattern as revealed by microscopic examination of tissue from many different areas of the tumor. It would be difficult to overemphasize, also, that one cannot have an adequate understanding of any particular bone tumor without an adequate understanding of its x-ray picture as a reflection of the gross anatomy of the lesion.

To me, it seems that in the practical approach to bone tumor classification and diagnosis, one must conceive of the different tumors as clinico-pathologic entities toward whose delimitation age and sex distribution, localization, roentgenographic pattern, and dominant histologic pattern all contribute more or less. However, the presentation tonight relates to a general theory of the bone tumors. This theory is based upon the idea that all the different types of tumors originate from a single type of basic cell and that the differences which the tumors eventually present represent merely differences in the degree to which the cell has come to approximate full functional capacity. The corollary of this idea is that the only justification for different names for the different bone tumor entities lies in a difference in clinical behavior. I admire the broad scope of Dr. Johnson's thought on this whole question. But it seems to me that this attempt to reduce the bone tumor problem to the idea of a basic cell played upon by the forces of growth and metabolism obliterates useful distinctions in its attempt to create unity.

Dr. Johnson gave us a clear and vivid summary of protein chemistry as it applies to bone formation, and a dynamic picture of the activity of the osteoblasts and chondroblasts in laying down bone and cartilage matrix. He also pointed up the metabolic interchange that goes on in the bones in general, and in various specific sites in individual bones. I am afraid, however, that all this does not help us as much as he thinks it might in the understanding of bone tumors. The trouble is that he bases much of his argument upon the idea of a close analogy between the physiologic activity and behavior of bone as tissue on the one hand, and the behavior of the tumor tissue of a tumor in bone on the other. Actually, many of the tumors which he forces into a unit on this basis are of fundamentally different natures. This is true, for instance, of multiple myeloma on the one hand, and osteogenic sarcoma and chondrosarcoma on the other. Nevertheless, it is always good to be made to see so vast a subject again as a whole. And this Dr. Johnson has done for us.

FRED W. STEWART: I did not intend to discuss this paper. I spent a week in Washington at the Institute in December, and talked this over with Dr. Johnson and saw some of his material, and I think I was rather more impressed than Dr. Jaffe seems to have been. I feel in fact very sympathetic with his point of view, and I must also say I do not think he has made the effort to destroy or render useless the various existing clinical-pathologic distinctions. He admits their validity.

LENT C. JOHNSON: I wish to thank Dr. Jaffe and Dr. Stewart for their remarks.

In reply to Dr. Jaffe, may I emphasize that statements or implications as to the cell of origin for any of these tumors were carefully avoided. In fact, it was specifically stated that the cells were identified only by their products, that is, descriptively. The cell of origin, like paternity, is often a matter of faith, while the descriptive designation of a cell need not involve commitments regarding its past or its future. This attitude is necessary when within a single slide of the whole tumor from a uterus one can find a leiomyoma undergoing sarcomatous transformation to a myosarcoma and then extensive metaplasia to produce bone. When the bulk of such a tumor is composed of bone, it is descriptively an osteosarcoma, but histogenetically, metaplasia of a myosarcoma. Only the accident of a fortunate section established an unexpected cell of origin. Since this accident seldom occurs in bone tumor, or in tumor slides in general, ideas of cell of origin are still largely a matter of inference and faith. The table demonstrating the relationship between the tumors is not a table of derivation from a cell of origin but of functional and chemical kinship, irrespective of cell of origin.

Dr. Jaffe has properly warned against mistaking tissue elements in a tumor for the actual products of the tumor cells. In all the illustrations that I have shown, a critical selection was made to demonstrate only those matrices that meet the criteria of production by the specific neoplastic cells.

I am certainly in complete agreement with Dr. Jaffe's statement that tumor diagnosis depends on the dominant histologic pattern and that x-ray and clinical correlations are necessary. However, our object this evening was to consider the possible meaning of the subdominant or minor patterns that are also to be found in many tumors. The situation is analogous to the circumstances in the physical sciences after the formulation of the laws governing the behavior of gases in a room such as this. Later studies demonstrated that these laws did not adequately account for the behavior of gases at extremes of temperature and pressure. This led to modifications, from which evolved a single general law and a deeper insight into the molecular behavior of gases that was not possible until the exceptions had been understood. Yet, the new equations, the new laws, which encompassed the exceptions, in no way invalidated the operation of the original gas laws at room temperature. Likewise a consideration of the relationships between tumors in no way modifies the need for, or the criteria of every day hospital diagnosis. It may, however, give us added insight into the reasons for the behavior of each tumor. It also presents us with challenges to additional investigations that are not otherwise apparent: for example, if the field within which a tumor arises determines its cell type, speed of growth, and manner of spread, a proper understanding of the biologic laws which govern that field might lead to the means of control of the cells and eventually might permit conversion of bone tumors from more active to less active and even to manageable types.

This attempt at a general theory does not stand alone but is in keeping with the work in other classes of neoplasms. It is the essence of Bailey and Cushing's original work on gliomas and of Kernohan's more recent study, of Dr. Foot's studies of skin tumors here in New York, and of Friedman's and Moore's study of testicular tumors. Paradoxically, boundaries between individual tumors in each category become indistinct as our perception sharpens. One may reasonably hope that general theories of each major class of tumors may pave the way for a general theory of all neoplastic diseases.

New Optical Methods For the Study of the Cell: Applications in Pathology

ROBERT C. MELLORS

Sloan-Kettering Institute for Cancer Research and Pathology Laboratories, Memorial Center, New York

The analysis of micro-microgram (10^{-12} gm.) quantities of certain biochemical compounds, such as cyclic amino acids, purines and pyrimidines, nucleic acids, porphyrins and steroids, can be performed by instrumentation which employs the reflecting microscope and accessory optical and electronic components. Microabsorption analysis can provide qualitative, identifying information, such as the presence of absorption bands at 416.0, 538.7, and 574.4 m_μ for the oxyhemoglobin contained within a single red blood cell, and quantitative data, such as the amount of hemoglobin in a single red blood cell, 30×10^{-12} gm. or the desoxyribose nucleic acid content of a single cell nucleus, a value of the order of 6×10^{-12} gm.

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2. The localization of the iron-protein complexes, ferritin and hemosiderin.
3. The composition of renal tubular casts in cholemic and hemoglobinuric nephrosis.
4. The localization of fluorescent carcinogens.
5. The nucleic acid content of the normal and the neoplastic cell.
6. The activity of oxidative enzymes in the mitochondria of living cells.

DISCUSSION

MARY A. MARCUS: Is there any evidence that one can identify viruses by this means?

THOMAS G. MORRIONE: Dr. Mellors, what is the degree of accuracy of these quantitative methods?

ALFRED ANGRIST: Can the system be adapted to a fluorescent screen?

ROBERT C. MELLORS: A discussion of the identification of viruses is a subject which would take us far afield. Optical methods that we have described here would not be useful in such a study because, in general, viruses are too small to be observed by this type of microscope. The electron microscope, of course, has great applicability in the study of small particles such as viruses.

The question of accuracy can be answered by saying that the micro-method does not have the accuracy of a macro-method. It is most difficult to express this as a per cent figure without much qualification and detail.

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1. Hechter, O.; Dopkeen, S. K., and Yudell, M. H.: The Clinical Use of Hyaluronidase in Hypodermoclysis, J. Pediat. 30:645 (June) 1947.

2. Schwartzman, J.; Henderson, A. T., and King, W. E.: Hyaluronidase in Fluid Administration: A Preliminary Report, J. Pediat. 33:267 (Sept.) 1948.

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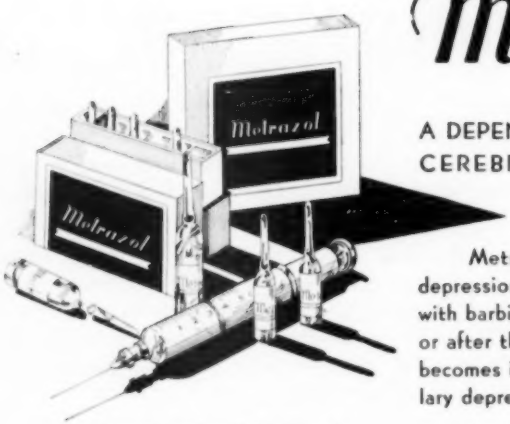

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2. Behrman, H. T., Combes, F. C., Bobroff, A. and Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.

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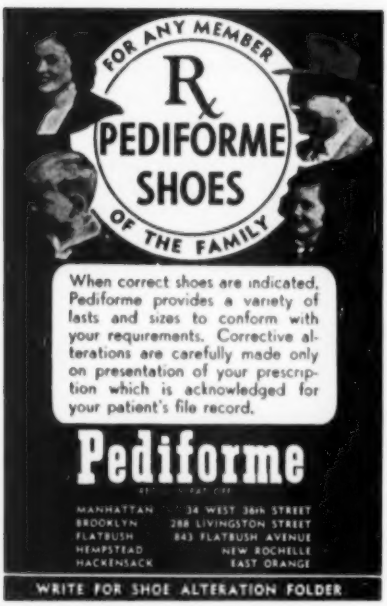
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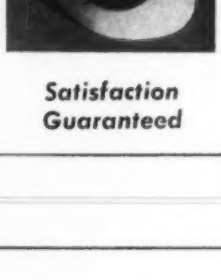

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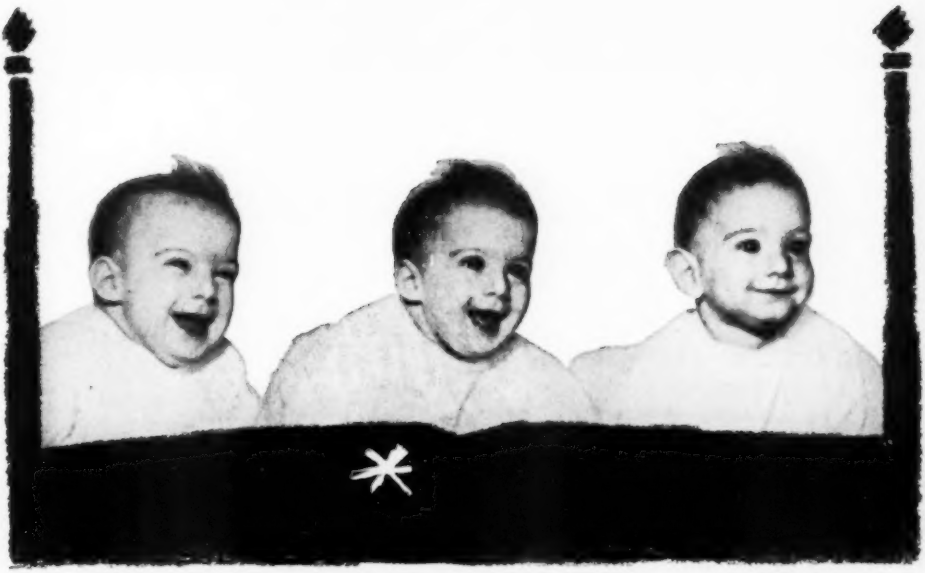

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*Sobel, S. H.: Milk Allergy in a case of Triplets, *Clin. Med.*, August 1952.

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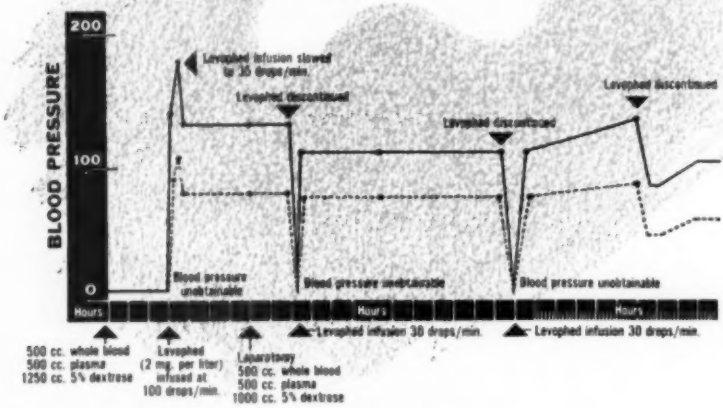

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Bibliography

1. Hitch, J. M.: North Carolina M. J. *12*:548, 1951.
2. Peck, S. M., and Michelfelder, T. J.: New York State J. Med. *50*:1934, 1950.
3. Couperus, M.: J. Invest. Dermat. *13*:35, 1949.
4. Sofer, A.: Quart. Rev. Int. Med. & Dermat. *8*:1, 1951.
5. Johnson, S. M., and Bringe, J. W.: Arch. Dermat. & Syph. *63*:708, 1951.

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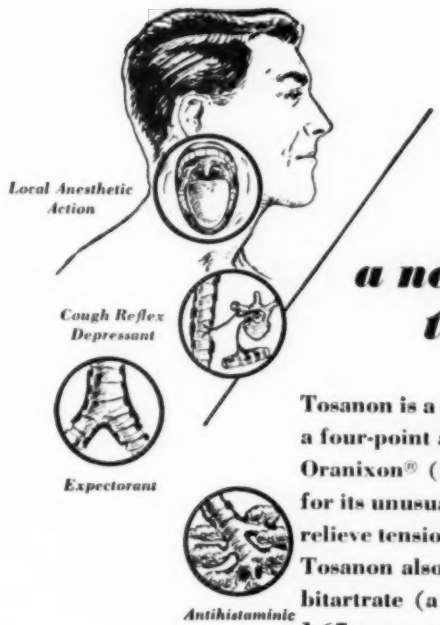

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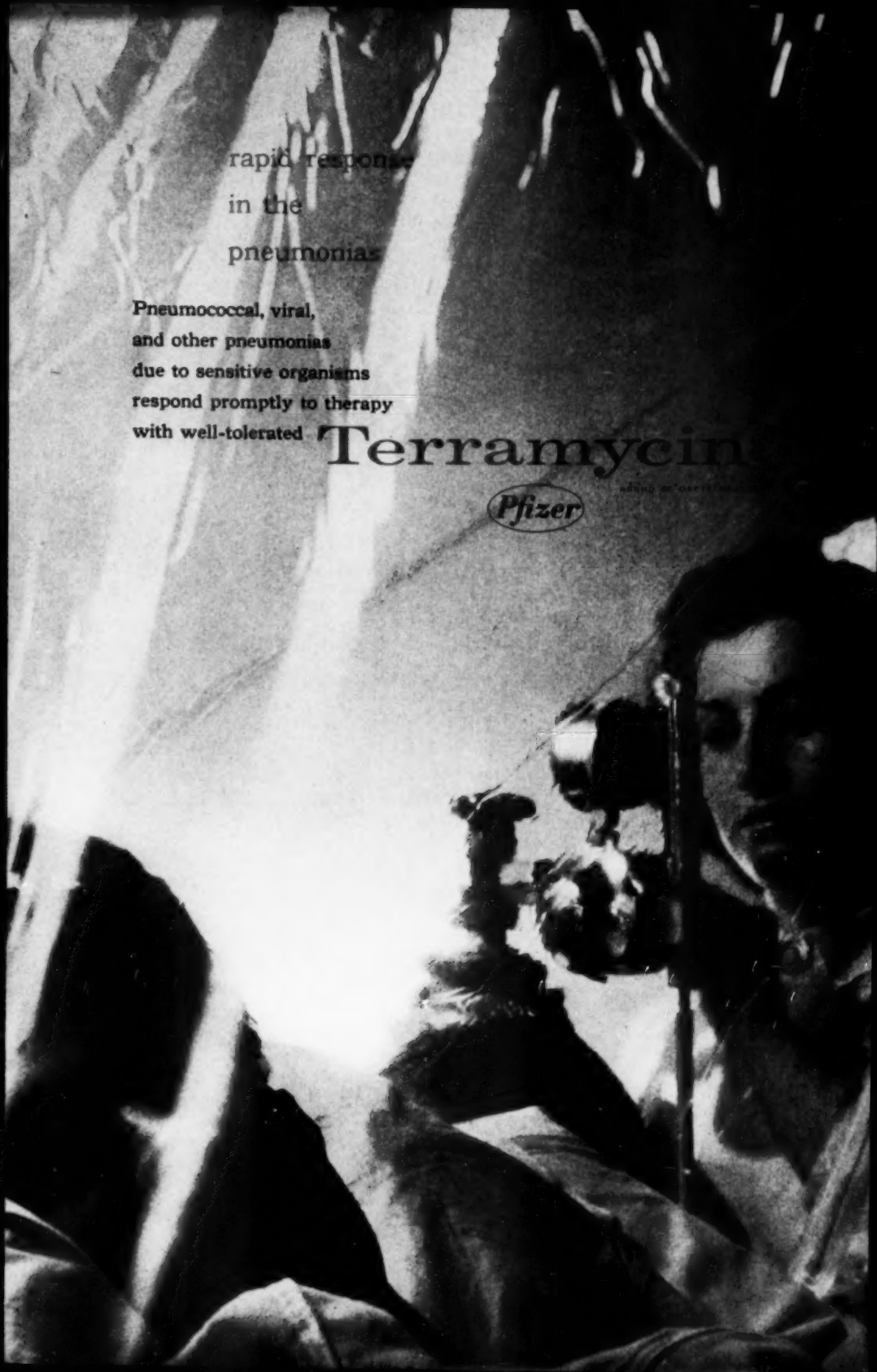
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prescribed for a lifetime...

NEOHYDRIN*

THE DIURETIC TABLETS THAT WORK LIKE AN INJECTION

lifetime therapy—

NEOHYDRIN helps keep the cardiac patient in fluid and electrolyte balance for his lifetime—a lifetime that might be impossible without such control of water and salt metabolism.

day in, day out diuresis—

NEOHYDRIN daily, maintains a steady, uninterrupted diuresis. This allows more liberal salt intake which benefits the patient psychologically. Even more important, liberalized salt intake permits the daily physiologic intake and output of sodium required by the body and safeguards against salt depletion.

how to use this new drug

Maintenance of the edema-free state has been accomplished with as little as one NEOHYDRIN Tablet a day. Often this dosage of NEOHYDRIN will obtain per week an effect comparable to a weekly injection of MERCUHYDRIN.® When more intensive therapy is required one tablet or more three times daily may be prescribed as determined by the physician.

Gradual attainment of the ultimate maintenance dosage is recommended to preclude gastrointestinal upset which may occur in occasional patients with immediate high dosage. Though sustained, the onset of NEOHYDRIN diuresis is gradual. Injections of MERCUHYDRIN will be initially necessary in acute severe decompensation.

NEOHYDRIN is contraindicated in acute nephritis and nephrosclerosis.

Any patient receiving a diuretic should ingest daily a glass of orange juice or other supplementary source of potassium.

prescribe NEOHYDRIN when indicated in

congestive heart failure • recurring edema and ascites • cardiac asthma • hypertensive heart disease dyspnea of cardiac origin • arteriosclerotic heart disease • fluid retention masked by obesity • and, for patients averse to their low-salt diet.

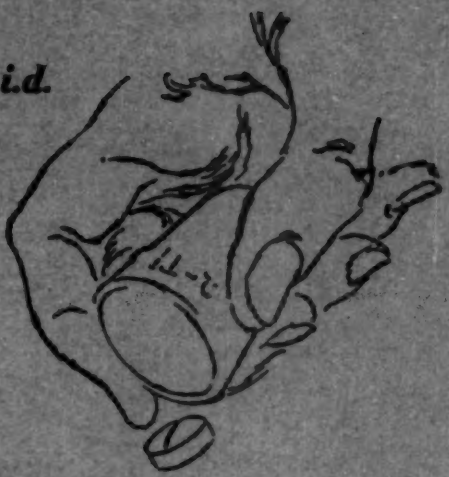
packaging Bottles of 50 tablets. There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea in each tablet.

Leadership in diuretic research ®-4

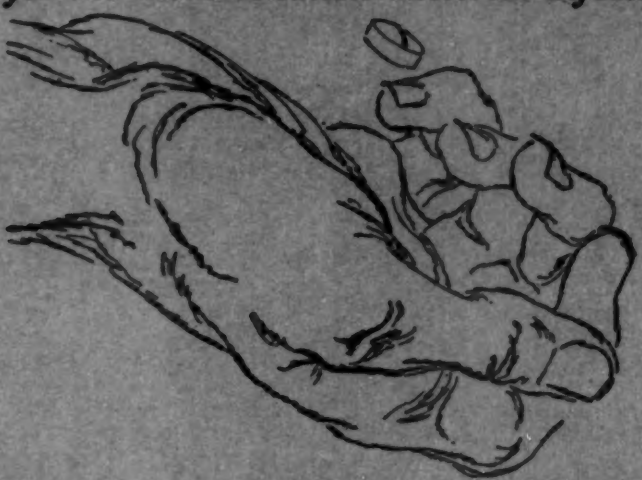
Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

*TRADEMARK APPLIED FOR

oral penicillin t.i.d.



. . . for the more common bacterial infectious diseases



Just 1 or 2 Pentids Tablets t.i.d. are particularly effective . . . convenient, easy-to-take . . . cause fewer side effects . . . and are less than ½ the cost of the newer antibiotics.

Bottles of 12 and 100.

formulated for convenient t.i.d. dosage

Pentids

Squibb 200,000 Unit Penicillin Tablets

SQUIBB